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NETHAPHYL IN THE TREATMENT OF NASAL ALLERGY AND BRONCHIAL ASTHMA

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IN the management of nasal allergy, allergic bronchitis and bronchial asthma, certain drugs must be prescribed to give the patient symptomatic relief. This is particularly necessary during the period of observation and study of the allergic problem involved. Sometimes it is necessary, especially in difficult cases, to continue to use drugs for an indefinite period of time. It is particularly desirable to use those preparations which are most effective, have the least side effects and to which there is little or no tendency to increased tolerance. The following clinical observations represent a supplemental report to that presented four years ago on the use of Nethaphyl.[14] During a period of seven years 47,000 tablets of this preparation and 24,400 tablets and capsules of the same with the addition of phenobarbital were dispensed to 750 patients, 150 of whom were children.

In the previous report, the pharmacology of the above preparations was presented in detail. It should be sufficient, therefore, to review only briefly the essential characteristics of these preparations.

NETHAMINE HYDROCHLORIDE

This preparation is chemically methylethylamino-phenylpropanol and has essentially the pharmacological action of ephedrine. The degree of action in the bronchioles and the respiratory stimulation is the same, whereas it produces no noticeable pressor action and only a minimum degree of central stimulation.[1] Craddock[4] has shown that nethamine, in a series of eleven allergic patients sensitive to ephedrine and adrenalin or both, produced efficacious results and was tolerated without any undesirable side actions in all but one patient. Friedman and Cohen,[5] com-

"Nethaphyl" is a registered trademark of The Wm. S. Merrell Company for a combination of Nethamine (methylethylamino-phenylpropanol) Hydrochloride and Butaphyllamine (theophylline aminoisobutanol).

pared nethamine with ephedrine in forty-six allergic patients and found that the toxic effects were much more numerous with ephedrine, particularly in regard to central nervous stimulation. Clinically, nethamine seemed to be as efficacious as ephedrine but with much fewer side actions.

BUTAPHYLLAMINE

This preparation is chemically theophylline aminoisobutanol and offers certain improvements in stability and solubility in comparison to other compounds of similar nature. It contains approximately 67 per cent theophylline and the toxicity in the experimental animal is approximately of the same order as that of aminophyllin.[13] Steinberg and Jensen,[11] in studying the use of this compound in angina pectoris, found it to be somewhat better tolerated than other theophylline compounds. Smith and Jensen[10] demonstrated its value in experimental heart failure in producing striking stimulation of the myocardial contractions and in causing rapid removal of the pulmonary edema and congestion resulting from heart failure experimentally induced. Steinberg and Jensen,[12] in a later report, demonstrated that theophylline aminoisobutanol caused a fall in venous pressure and a shortening of circulation time. These effects were more pronounced when these functions were elevated above normal.

These studies seem to indicate that butaphyllamine has the basic action of other theophylline derivatives with the possible advantages of better toleration.

THEOPHYLLINE DERIVATIVES IN ASTHMA

The pharmacologic basis for the use of theophylline preparations in the treatment of bronchial asthma was demonstrated by Young and Gilbert.[14] In a clinical study of sixteen patients, Herrmann and Aynesworth[7] employed the intravenous route of administration. They made the observation that in one patient in whom the injection failed to give relief, adrenaline was of benefit as a subsequent injection although the patient had been previously refractory to it. Hyman[8] also made this observation. Theophylline apparently overcomes the refractoriness to adrenalin. Carr[3] and also Brown and Blanton[2] reported the effectiveness of theophylline preparations in adrenalin-fast patients.

In a critical study on the use of theophylline mono-ethanolamine in the treatment of bronchial asthma and other allergies, Lamson and Bacon[9] presented their observations on a group of 153 patients. They recommend the administration of the smallest effective dose, to be repeated only when necessary. Small doses minimize unpleasant side effects. Adrenalin-fast patients responded satisfactorily, and after one year it was not necessary to increase the dosage to obtain the same degree of relief. In a group of 112 patients, 77 per cent had definite and complete relief of symptoms on a total dose of 0.26 Gm. or 4 grains in twenty-four hours. Untoward side effects were inconspicuous. Gnaw-

ing sensation in the epigastrium, nausea and sometimes vomiting were the chief untoward effects, but these did not occur when the medication was taken with food. Occasionally tachycardia occurred.

CLINICAL OBSERVATIONS

The following observations are based upon a study of 750 cases of allergic bronchitis and bronchial asthma in which nethamine and butaphyllamine were employed as an adjunct in allergic management. One hundred fifty of the 750 patients were children varying in age from two to fourteen years. These studies were conducted over a period of seven years, during which time the following were administered: Nethamine ¾ gr. and butaphylline 2 gr., 38,400 tablets; nethamine ¾ gr. and butaphylline 1 gr., 8,600 tablets; nethamine ⅜ gr., butaphylline 1 gr. and phenobarbital ¼ gr., 18,400 capsules and nethamine ¾ gr., butaphylline 2 gr. with phenobarbital ¼ gr., 6,000 tablets. Inasmuch as the majority of patients, especially the children, had nasal as well as bronchial symptoms, the combination of the two drugs was found to be more satisfactory than using the latter alone.

In a significant number of patients with chronic cough, without definite nasal symptoms or bronchial asthma, the cause may be explained on an allergic basis. In children there is not infrequently a history of chronic cough before the onset of definite asthma. None of these patients is satisfactorily relieved by the usual cough mixtures containing narcotics.

We have found that these patients usually responded to the administration of nethamine and butaphyllamine suggesting an allergic cause which could be proved by an allergic investigation.

The results obtained in this series of cases confirm those reported by others on the use of theophylline compounds in the treatment of bronchial asthma. On the whole, our studies were conducted on a basis similar to that reported by Lamson and Bacon[9] in that an attempt was made to establish the minimum effective dosage. At the same time, patients were instructed to take the medication only when necessary. When continuous administration was indicated, the doses were recommended every three to four hours. In general, the average optimum dosage in adults was nethamine ¾ gr. and butaphyllamine 1 gr. Some patients required twice this dosage, rarely larger. Those patients who complained of insomnia or palpitation were given the tablets or capsules containing in addition ¼ gr. of phenobarbital. The average dosage in children from four to twelve years of age was nethamine ⅜ gr. and butaphyllamine ½ gr. Occasionally it was necessary to double this amount. The length of time the medication was continued varied considerably in the entire group. Those patients who responded promptly to allergic methods of management were able to discontinue the medication within a short period of time. In the more difficult cases, in which response to man-

agement was slow or in the case of those patients who never became entirely free of bronchial asthma, the medication was continued for several years, the longest about seven years. In these instances, there was no tendency noted to increase tolerance to the medication.

The untoward side effects from this compound were clinically insignificant (or inconsiderable); epigastric distress, nausea or vomiting occurred only occasionally, but these reactions could usually be eliminated when the medication was taken with food or the dosage decreased. Unlike ephedrine combinations, this product rarely produced palpitation and only occasionally did the patient experience insomnia. The very infrequently occurring nervousness and insomnia could easily be controlled by the administration of the tablets or capsules with phenobarbital added. A number of patients could take nethaphyl who could not tolerate ephedrine combinations. So far no case of sensitivity to nethaphyl has been observed.

In the treatment of bronchial asthma, nethaphyl is far superior to benadryl, pyribenzamine and similar preparations. Although the latter compounds have been very effective in the relief of hay-fever symptoms, the observation has been made by a number of allergists that complicating asthma more frequently occurs from over-use of these drugs. Prolonged vasoconstriction of the nasal mucosa apparently decreases the filtering function of the nose as a result of which more pollen enters the bronchial tree.

SUMMARY

1. A study of the use of nethaphyl (nethamine hydrochloride, and ephedrine-like compound, and butaphyllamine, a theophylline derivative) in the treatment of nasal allergy and asthma in 750 patients extending over a period of seven years is reported.

2. The effectiveness in the relief of symptoms has been most satisfactory.

3. Untoward side effects were inconspicuous.

4. Minimum or optimum doses are recommended.

5. Repeated administration has not necessitated an increase in dosage.

6. On account of the high solubility of these drugs, absorption is rapid and responsiveness is prompt.

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ASKS AID IN NURSING CRISIS

Katharine J. Densford, president of the American Nurses' Association, has urged the governors of all forty-eight states to call state-wide conferences "at the earliest possible date" to consider concrete measures to resolve the nursing crisis created by increased demands for nursing service now facing the American public.

Pointing out that the nursing profession is united on a program of action, Miss Densford, in telegrams to each governor, called for effective action in every state of the union. Her message follows:

"I made a nation-wide telephone roll call from Minneapolis on October 20 to get the support and co-operation of the forty-eight presidents of the state nurses' associations. The ANA, representing 155,000 professional registered nurses, received wholehearted support from the state association presidents on three major points of the ANA's program: (1) Make nursing care equally available to all by intensifying efforts of the ANA's counseling and placement service for the best possible use of available nursing service, and provide a continuing supply of nurses by promoting recruitment; (2) improve nurses working conditions, rates of pay, personnel practices, and see that nurses share in the administration of nursing services; (3) protect the public by adequate legal control of nursing practice, both professional and practical.

"We in ANA are doing everything in our power to rouse the public to a clearer understanding of the nursing crisis, because nurses cannot singlehandedly solve the problem. Effective action is needed at once in every state of the union. As president of the American Nurses' Association I am respectfully requesting the governors of each state to co-operate with us.

"Specifically, I ask you to call on the president of your state nurses' association, and the head of every group interested in public health and public service, to meet at a state-wide conference under your auspices at the earliest possible date to consider concrete measures resolving the nursing crisis now facing the American public. I shall deeply appreciate a prompt reply from you indicating what co-operation you can give this public situation."

THE SKIN-TEST BLOCKING ANTIBODY RESPONSE TO ORAL POLLEN THERAPY AND THE CRITERIA FOR ITS USE

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With the Technical Assistance of
MISS HELEN A. FLAHERTY

SINCE its initiation by Noon in 1911, no other form of treatment has seriously challenged the position of injection therapy for the treatment of pollen sensitivity. The presence of immunological changes following the injection of pollen extract has been demonstrated by Harley[11] and measured by a number of workers; chiefly by Loveless[17-21] and by Cooke and Sherman.[7] Exact correlation between antibody titer and clinical improvement has, however, been questioned by Black[4] and others, and it is the present opinion that such relationships are highly individual. Although there is no doubt that the heat-stable blocking antibody appears as a result of injections of pollen extract, there is no certainty that either its presence or its quantity is a measure of immunity, especially since injection treatment is known to cause simultaneous increase in the reagin content of the blood of some subjects. The degree of hyposensitization may therefore lie in the proportional increase of what appears to be a double type of response to a single botanical, but actually an immunologically multiple biochemical stimulus.

Unsatisfactory as the present state of our knowledge may be for injection therapy, that of oral pollen treatment is, if anything, less satisfying, since the results reported are almost entirely clinical.

Gatterdam,[10] using a phosphate glycerin pollen solution, given orally, reported that his patients achieved 90 to 100 per cent relief. Hartmann[12] tabulated excellent results following the use of tablets composed of the seeds and flowers of plants causing hay fever. Rockwell,[22,23] who stated that oral pollen dosage should be 50 to 100 times greater than that given by injections, was able to demonstrate satisfactory results in 115 patients, with fair results in twenty-three, and no relief in forty-four. Greater improvement was described by Schwartz,[24] of whose sixty-five patients, 40 per cent were completely relieved, and 47 per cent satisfactorily relieved, while only 13 per cent had poor results. Conway,[6] with 1,600 patients, reported 94 per cent as completely free of symptoms.

The negative reports are equally impressive. Bernstein and Feinberg[3] observed that the gratifying results were achieved in areas of low pollen concentration. Of their twenty patients treated co-seasonally with oral pollen, eighteen were complete failures. The asthmatic patients did not respond in any measurable degree. Of forty patients studied by Black[4]

The expenses incurred by this study were defrayed, in part, by The Asthma Research Foundation, Inc., of Boston, Massachusetts.

only 40 per cent demonstrated satisfactory improvement. Three of these who were unable, at first, to take hypodermic injections, after pollen ingestion tolerated injection therapy. Alperstein[2] was able to show that oral therapy was more effective in those who had previously been given injections as compared with those who had no previous treatment. His comparisons, however, show injection treatment as much more satisfactory, although oral treatment gave, in some patients, considerable relief. In a later co-operative study, Feinberg and his associates[9] demonstrated that occasional patients, given placebos, reported results comparable to those taking pollen orally. Iliff and Gay[14] and Bohner[5] concurred that injection therapy was the more satisfactory form of treatment.

Although Eyerman[8] has suggested that any type of therapy must be applied to the same patient for at least five years before its value can be estimated, an analysis of these reports, limited at the most to one season, demonstrates that although the consensus favors injection treatment, the results with both forms of therapy illustrate the well-known clinical fact that patients do both poorly or well on both high or low doses of both the injection or oral types of treatment. It occurred to us that it might be possible to advance our clinical knowledge if immunological procedures could be used to demonstrate other than clinical responses to oral pollen therapy.

It has been shown by Loveless *(op. cit.)* that the blocking antibody appeared as a result of injection treatment. Alexander and his associates,[1] confirming its presence, stated that generally the relief from hay fever seemed to be due to a high thermostable antibody titer. In their subjects, the reagin titer was not correlated to the thermostable antibody of circulatory antigens. On the other hand, Scully and Rackemann[25] had concluded earlier that no correlation could be found between the amount of blocking antibody produced as a result of treatment and the clinical relief of symptoms, and that the therapeutic effects of ragweed extract therapy are not due to the production of such antibody. An examination of the techniques followed suggests that they differ from those first described by Loveless.[18]

There are also differences of opinion concerning the effects resulting from the ingestion of pollen. London[16] failed to find any evidence of the presence of ragweed pollen protein in the blood stream following its oral administration. Zeller[27] concluded that the only available evidence of enteral absorption of pollen is the constitutional reactions which are encountered following its ingestion. Thiberge,[26] who tested sensitive subjects intracutaneously with both ordinary pollen extracts and extracts artificially predigested with gastric, intestinal and pancreatic enzymes, concluded that gastric digestion destroys some of the antigenic power of ragweed pollen. Hecht[13] and his co-workers, studied the reactions produced in passively sensitized skin sites, their results indicating that a relationship existed between the gastric acidity and the pollen absorption. Sixteen patients

with low acid values absorbed sufficient pollen to produce reactions in passively sensitized sites, while six with normal acid values did not absorb sufficient antigen to produce reactions. Of interest in this report is the work of Levin and Shulsky,[15] who showed that eleven of thirteen children, injected hypodermically with ragweed pollen, demonstrated an increase in the neutralizing capacity of the serum and nine showed an increase in the skin sensitizing ability of the serum. In ten children treated orally (240,000 Noon units daily), nine showed an increase in the neutralizing capacity of the serum and all ten showed an increase in the skin sensitizing ability of the serum. The results therefore indicated that pollen taken orally in adequate quantities is absorbed from the gastrointestinal tract and that the succeeding changes are similar to those occurring in patients treated hypodermically.

The conclusions drawn from the literature indicated that further work in this field appeared to be warranted.

In all, twenty patients were chosen for study. Of these, six ceased treatment, leaving fourteen who could be used for investigative purposes. Of these, nine were male, of whom five had hay fever and the remainder both hay fever and bronchial asthma. Of the six females, only one suffered from an uncomplicated hay fever, and five both from hay fever and bronchial asthma. The ages ranged from nine to twenty-five, with one patient aged forty-two and one aged sixty. All had had symptoms for more than one season, but none had had either skin tests or injection treatment. For all of the subjects studied, the history was taken by one worker, the treatment given by a second, and the serum titrated by a third. The skin and conjunctival tests were done by a skilled technician, who also took blood for titration purposes before skin-testing the patient for the first time, and subsequently during the treatment period, as well as following the cessation of treatment. The patients reported on their progress and also kept symptom diaries. In order to discover whether the oral pollen therapy would affect the skin tests, all of the patients were tested on the occasion of their first visit, and on three or more subsequent visits. The tests were done intracutaneously and with fresh extract standardized in PNU. So that minor changes could be measured, the successive gradations were made smaller than usual, the strength in units measuring 0.05, 0.1, 0.5, 1, 5, 10, 50, 100, 150, 200, 350, 500, 750, 1,000, 1,500, 2,000, 3,500, and 5,000 units. A wheal with pseudopodia and a flare was defined as a positive reaction and in each case a test was done with higher concentrations, in order to corroborate the positive reactions. Conjunctival tests were done with increased concentrations; 100, 150, 200, 350, 500, 750, 1,000, 1,500, 2,000, 3,500 and 5,000 PNU of freshly prepared ragweed pollen extract, the less injected eye being chosen.

Blood was taken on the first visit and before the patient was tested, and on subsequent days during the treatment period and during the ragweed

pollen season and in seven patients two to three months post-seasonally. The blood was taken at least three days following pollen ingestion. The serums were labeled A and P_1, P_2, and P_3. The technique followed for antibody titration is essentially that described by Loveless[18] and by our previous communication to this journal (Ann. Allergy, 2:207, 1944).

The rationale of the technique is based upon the fact that the quantity of the immune antibody present in the serum of a treated allergic patient can be measured by two methods. The first is an estimation of the capacity of the serum to inhibit the reaction which would naturally occur when a passively sensitized subject is tested with free antigen. If the antigen is completely bound, no reaction will occur, but in such sites in which reactions do occur, the degree of response will be proportional to the amount of immune antibody present. Secondly, the same sites can be reinjected with an excessive amount of antigen. In those sites, in which the first antigen injection was bound and completely inactivated, the reagin is still present in its original amounts and the injection of excessive antigen will produce a maximum reaction. In those sites in which the antigen first injected was not completely inactivated so that some combination of reagin and antigen occur, there would be a lesser amount of reagin present. The injection of an excessive amount of antigen would result in a noticeably smaller reaction. For quantitative studies, all sites are sensitized with equal amounts of the same ante-treatment serum. To maintain the reagin content of all the sites equal when post-treatment serum is added, the contained reagins are destroyed by heating at 60° C. for one hour.

The tablets used were prepared for us by Brewer and Company (Worcester, Mass.) and were made to contain sufficient pollen to be equivalent to 1,000, 10,000, and 30,000 PNU with an enteric coating designed to disintegrate in the alkali of the small intestine three to five hours following ingestion. They were colored red, white, and blue, so that the respective strengths could not be mistaken. Each patient received initially twenty-four red tablets, with instructions to take one, two, three, four, six, and eight tablets after the largest daily meal at three-day intervals, the days being termed as one, four, seven, ten, thirteen and sixteen. The successive doses were therefore 1,000, 2,000, 3,000, 4,000, 6,000 and 8,000 PNU. On his return, if no symptoms referable to the gastro-intestinal or respiratory tracts had occurred, the patient received twenty-four white tablets, one to be taken on that day (the nineteenth) and then every third day to the forty-third day; two tablets (20,000 PNU) on the twenty-second day; and thereafter three tablets (30,000 PNU) for each successive dose every three days. On the patient's third visit, twenty-four blue tablets, each representing 30,000 PNU, were dispensed, one tablet to be taken that day, two tablets three days later, and three tablets (90,000 PNU) every third day thereafter. By the seventy-second day, the patient had taken seventy-two tablets representing a minimum dose of approximately

TABLE I. DOSAGE SCHEDULE (PRESEASONAL)

Day	Dose	Total PNU Units	Color	No. Tablets
1	1	1,000	Red	1
4	2	2,000		2
7	3	3,000		3
10	4	4,000		4
13	5	6,000		6
16	6	8,000		8
19	7	10,000	White	1
22	8	20,000		2
25	9	30,000		3
28	10	30,000		3
31	11	30,000		3
34	12	30,000		3
37	13	30,000		3
40	14	30,000		3
43	15	30,000		3
46	16	30,000	Blue	1
49	17	60,000		2
52	18	90,000		3
55	19	90,000		3
58	20	90,000		3
61	21	90,000		3
64	22	90,000		3
67	23	90,000		3
70	24	90,000		3
72 days	—24—	984,000 PNU		72 Tablets

1,000,000 PNU. Some patients continued the blue tablets, taking three at mealtime for some weeks or months longer, reaching a maximum of 6,000,000 to 7,000,000 PNU. The dosage schedule is tabulated in Table I.

The exact technique for the immunological studies can be outlined as follows:

1. The "A" (ante-treatment) serum was collected before the patient's first skin tests for ragweed pollen sensitivity were done. The serum was then stored in the ice box. Hinton reactions and bacterial cultures insured sterility. No experiments were performed during the pollen season.

2. The "P" (post-treatment) serum specimens were collected according to the dates on the accompanying table, the first date being that of the skin tests, and the other dates at widely separated intervals, including one, whenever possible, during the pollen season, and another several months later.

3. The "P" serum was heated for one hour at 60° C. in a constant temperature bath, in order that all demonstrable skin sensitizing reagins might be destroyed.

4. The vials were set up in series, with chemically clean sterile 0.25 ml. pipettes. One series of vials was instilled with mixtures of constant amounts of autogenous serum "A" and progressive dilutions of the ragweed extract; another series with mixtures of constant amounts of autogenous serum "A," heated serum "P," and the progressive dilutions of ragweed extract. Saline was added to the first series to keep the volume relationships constant in all testing mixtures. The "A" serum added to the heated serum in the second series is, in almost every instance, the patient's own "A" serum. Two volumes of buffered saline were added to the serum used in the control mixture. After the ingredients were mixed, the vials were permitted to stand for one hour.

5. Using the skin on the back of the test subject, known by history and skin tests to be nonatopic, 0.1 ml. from each vial was injected for a series of ten sites. These sites are 3 inches apart and do not come within 2 inches of the spine. A graduated 1 ml. tuberculin syringe is considered sufficiently accurate for performing the injections. The test subjects are not used more than once.

6. The reactions are read at fifteen to thirty minutes, within which period the serum control sites are practically negative. In some instances, however, the nonspecific irritation did not subside before the specific reactions reached their maximum.

7. After twelve to eighteen hours, when practically all signs of the first test had disappeared, each test site was reinjected with 0.025 ml. of the dilution of ragweed extract containing 10,000 PNU/ml. For these injections, a 0.25 ml. tuberculin syringe was used, the needle point being inserted into the same puncture orifice produced by the previous sensitizing injection.

8. The reactions were observed at ten-, twenty-, thirty- and forty-minute intervals. When the nonspecific reactions appeared minimal and the specific reactions maximal, the sites were graded as 1, 2, 3, or 4 plus. The sites were then traced and photographed. The titer of the given unheated serum, or a mixture of this serum with a heated serum, is expressed in a number of units of antigen originally present in the site, which, on subsequent testing, gave a plus-minus reaction. The last positive reaction, or plus-minus reaction, is taken for the end point. This was done to make certain that an end point was not taken too far beyond the first negative response attainable. The technique given above is similar to that given in our earlier paper on this subject *(loc. cit.)*.

Analysis of the clinical results, taken from the patient's own impressions, shows seven who claimed no or slight improvement, and of an eighth who could not be certain of change and who is, therefore, classified with this group. In this same group, one patient stated that it was the worst year he had ever suffered. Six other patients concluded that they had had slight symptoms, some commenting that the treatment had given them excellent results.

It was thought that the data could be studied more effectively if the patients were classified as either very much improved or very much worse rather than trust our judgment to what might be a moderate or fair response. Any symptoms termed more than slight were considered as a poor result. Irrespective of the clinical results, immune bodies were present in only one ante-treatment serum, which consistently required 10 units of ragweed pollen extract for neutralization in each of three tests. In all of the others, no antibodies were present before treatment. In all of the patients, however, without exception, oral pollen ingestion caused an increase in heat stable blocking antibody, requiring for its neutralization an amount of antigen equivalent to a solution varying from 25 to 1,000 PNU. It can therefore be concluded, although tentatively, that pollen ingestion does cause the development of a blocking substance which does not apparently differ from heat stable blocking antibody. The relationship of its presence and amount to the patient's clinical symptoms is, however, not clear.

The first two patients in the second table (C. H. and M. W.) presented final respective responses of 25 and 50. Each claimed poor results, the second stating that he had had the worst year he had ever experienced. The third patient (R. P.), for a titration point of 50, reported only slight symptoms and much improvement.

TABLE II.

Patient	Date of serum collection	PNU antigen required to neutralize 1 ml. "A" serum	PNU antigen required to neutralize 1 ml. "A" serum and 1 ml. heated "P" serum	PNU antigen required to neutralize 1 ml. "A" serum	PNU antigen required to neutralize 1 ml. "A" serum and 1 ml. heated "P" serum	PNU antigen required to neutralize 1 ml. "A" serum	PNU antigen required to neutralize 1 ml. "A" serum and 1 ml. heated "P" serum
L. H.	2.14.44	0					
	4.24.44		0				
	6.26.44			0	10–25		
	8. 7.44					0	25
M. W.	12.27.43	0					
	3.10.44		0–10?				
	3.27.44			0	25–50		
	8. 7.44					0	50
R. P.	12.13.43	0					
	5. 1.44		0				
	6.30.44			0	50		
	12.11.44					0	50
G. S.	12.27.43	0					
	3.11.44		0				
	7.17.44			0	100–250		
	11. 6.44					0	100
W. Ka.	12. 3.43	0					
	2.25.44		25				
	6. 6.44			0	100		
	12.29.44					0	100
M. B.	11.29.43	0					
	2. 7.44		0–10				
	6.19.44			0	50	0	250
	8.11.44						

W. Ko.	11.29.43	0	10–25	0	25	250
	2.11.44					
	6.16.44					
	8.21.44					
L. F.	12. 6.43	0	25–50	0	250	250
	2.21.43					
	11.25.44					
	12.22.44					
F. DeB.	11.29.43	0	10	0	50	100–250
	2.14.44					
	3.19.44					
	8.18.44					
M. H.	12.16.43	0	10–25	0	100	250
	2.18.44					
	6.30.44					
	12.15.44					
L. R.	12. 3.43	0	0–10	0	50	500
	2.14.44					
	8. 7.44					
	12. 1.44					
W. B.	12. 6.43	0	0–10?	0	50–100	500–1000
	2.21.44					
	4.28.44					
	8.11.44					
J. C.	12.13.43	10	25	10	100–25	500
	12.28.44					
	5. 1.44					
	10.10.44					
G. B.	12. 3.43	0	10–25	0	100–200	1000
	2.11.44					
	6.16.44					
	8.11.44					

The fourth and fifth patients (G. S. and W. K.), with end points of 100, reported excellent results, and the latter "the best year yet."

The next four patients (M. B., W. K., L. F., and F. DeB.), with titration points of 100 and 250, showed no improvement, while the tenth patient (L. H.) was much improved for the same immune response.

The eleventh and twelfth patients (W. B. and L. R.), for a response of 500 to 1,000, showed no improvement, while the thirteenth (J C.), for 500, claimed his best year. The last patient (G. B.), for 1,000, had great improvement. It is apparent that for each level of response there are both equally poor and excellent results. The titration reactions of a typical patient (M. H.) are demonstrated in the third table.

Is there a relationship to the patient's initial syndrome? Four subjects suffering from pollen hay fever and bronchial asthma showed no improvement, and four presenting the same syndrome, were markedly bettered. Three with simple hay fever reported no improvement, while three were noticeably free of symptoms.

Two patients complained of gastric upsets, and one additional subject stated that nausea and vomiting followed the ingestion of the tablets when three of the white were taken. She also felt that her bronchial asthma was much more severe on the day of medication.

One patient (G. S.) attributed a bout of diarrhea to the tablets, but continued their ingestion without further symptoms and reported an excellent season.

It was hoped that long-term studies could be done, but early in 1947 we were successful in discovering the present status of only five patients, four of whom took subsequent injection treatment with good results, while the fifth, who had achieved relief following oral therapy, was still doing well without treatment.

In the fourteen patients for whom there was sufficient data, correlations between skin tests, eye tests, antibody titer, and clinical results were sought.

For L. H., the successive intracutaneous skin tests at intervals of two months gave reactions at levels of 10, 50, 50, and 100 PNU, while conjunctival tests were respectively 200, 200, and 350 for positive reactions and negative at 5,000 PNU on one occasion for eight months of pollen ingestion. For a treatment total of 3,000,000 units and a titer of 25, there was no improvement.

For M. W., who had successive skin tests from December 27, 1943, to August 7, 1944, and reacted consistenly at the 30 PNU level for ophthalmic tests which reacted equally consistently at 50 to 100 PNU, there was a treatment total of 6,000,000 units and a titer of 50, with no improvement.

The third patient (R. P.) demonstrated a change in skin tests, reacting on December 3, 1943, to 200 PNU, on February 8, 1944, to 350 PNU, and on March 24, 1944, to 1,000 PNU. The tests were thereafter nega-

TABLE III. EXAMPLE OF TITRATION REACTIONS
Patient No. 10 (M.H.)

PNU	Initial		12-hr. Reinjection		Initial	12-hr. Reinjection	Initial	12-hr. Reinjection
	"A" Serum	"A"and Heated "P"	"A" Serum	"A" Serum Heated "PW"	"A"and Heated "P"	"A"and Heated "P"	"A"and Heated "P"	"A"and Heated "P"
10	3-4 plus	4 plus	exhausted	2 plus	2 plus	exhausted	1 plus	4 plus
25	3 plus	4 plus	0	1 plus	3 plus	3 plus	2 plus	3 plus
50	3 plus	4 plus	plus/minus	1 plus	2 plus	1-2 plus	3 plus	4 plus
100	4 plus	4 plus	plus/minus	1 plus	4 plus	plus/minus	3 plus	2 plus
250	3-4 plus	4 plus	1 plus	1 plus	4 plus	plus/minus	4 plus	plus/minus
500	4 plus	4 plus	1 plus	1 plus	4 plus	plus/minus	4 plus	plus 1
1000	4 plus	4 plus	1 plus	1 plus	4 plus	1-2 plus	4 plus	1 plus
1500	4 plus	4 plus	plus/minus	1 plus/minus	4 plus	1 plus/minus	4 plus	1 plus
Control	0	0	4 plus	4 plus	0	4 plus	0	4 plus

tive to solutions of 5,000 PNU. There was no ophthalmic test at any time and for a total dose of 4,000,000 and a titer of 50, he was much improved.

For the fourth patient (G. S.) the skin tests reacted at 0.5 PNU level and the ophthalmic test at 150 PNU. No further tests were done, but for a dose of 1,000,000 units and a titer of 100, he did exceedingly well.

The next patient in the series (W. Ka.) demonstrated progressive decreases in skin-test reactivity; his first initial test showing a response to 750 PNU on November 7, 1943, and a skin response only to 5,000 PNU on August 7, 1944. At no time was there a conjunctival test. For a total dose of 6,000,000 units and a titer of 100, he was much improved. (His "A" and "P" serums were graciously titrated for us by Dr. Mary Loveless, whose data showed a similar increase in titer, although her figures were higher than ours.)

On the other hand, M. B. demonstrated some change in skin reactivity; his test varying from an initial level of 100 PNU to a post-treatment reaction of 500 PNU. The conjunctival test was negative. For a total dose of 4,000,000 units and a titer of 250, there was no change in his symptoms.

Another patient (W. Ke.) demonstrated no change in skin tests, which remained at the 200 PNU level for ophthalmic tests which were constant at 500 PNU. For a total of 4,000,000 units and a titer of 250, there was no improvement.

For the next three patients, L. F. also presented no skin or ophthalmic test changes, the former remaining at 50 to 100 PNU and the latter at 350 to 500 PNU. With a total dose of almost 7,000,000 units and a titer of 250, he suffered severe symptoms. (For his serums, the titer as corroborated by Dr. Mary Loveless, was comparable to our own, although our end point was lower.)

For F. DeB., the skin tests and ophthalmic tests stayed at respectively 100 to 150 and 500 to 750 PNU. The total dose of 6,000,000 and a titer of 100 to 250 were associated with no improvement.

The tenth patient (M. H.) showed slight change in skin tests which

TABLE IV. A CORRELATION BETWEEN SKIN TESTS, EYE TESTS, AND CLINICAL COURSE

Patient	Skin Test Decreased	Skin Test Same	Eye Test Decreased	Eye Test Same	No Eye Test	Improved	Worse
1	X		X				X
2		X		X			X
3	X				X	X	
4						X	
5	X				X	X	
6	X				X		X
7		X		X			X
8		X		X			X
9		X		X			X
10	X		X			X	
11		X		X			X
12	X			X			X
13	X				X	X	
14	X—				X	X	

responded initially to 50 PNU and finally at 150, a probably insignificant variation. The ophthalmic test changed, however, from a reaction of 500 to one of 1,500. For a dose of 5,000,000 and a titer of 250, the patient claimed marked improvement.

The next patient (L. R.), with skin tests which remained stable at 50 to 100 and an ophthalmic test which varied in reactivity from 350 initially to 750 finally, for a titer of 500 and a dose of 6,000,000, showed no improvement.

The twelfth patient (W. B.) changed in skin-test reactivity from an initial 50 to a final 200 to 350 PNU level. The conjunctival test varied from 150 to 750 PNU, but for a dose of 6,000,000 and a titer of 500 to 1,000, there was no improvement.

The thirteenth patient (J. C.) apparently changed in skin-test reactivity, the successive levels of response being 150, 100, 1,000, 500, 1,000 PNU. There was no eye response. For a dose of 6,000,000 and a titer of 500, he claims his best year of symptom freedom.

The final patient of the series showed an unusual reversal, the successive skin test reactions being 100, 50, 1,000, 500, and 50. The ophthalmic test was negative. For a dose of 6,000,000 units and a titer of 1,000, he was much improved, both for his hay fever and bronchial asthma.

There are these variables to consider: Was the skin test increased or decreased? If an ophthalmic test was present, did it increase or decrease? Was there any relationship between these, the dose, the antibody titer, and the patient's progress?

An analysis of the data brings out the following suggestive conclusions: Two patients (M. H. and L. H.), whose skin test and ophthalmic test decreased were, one of them better for a titer of 200, and the other worse for a titer of 10. No valid conclusion can be drawn from two patients, but it might appear that the higher titer could perhaps represent a higher immunity.

Further studies show that in four patients in whom there was a decrease in the skin test and no ophthalmic tests were present, all improved,

although the titers were respectively 50, 100, 250, and 500. The absence of an ophthalmic test with a decrease in the skin-test reactivity is apparently associated with improvement, independently of the titer levels, although a fifth patient (G. B.), with a skin-test decrease, and then an apparent increase in sensitivity with no additional eye test and titer level of 1,000, was also among the improved.

In five patients, in whom the skin tests remained at the same level, the ophthalmic test was present and did not change, and in the sixth patient, in whom the skin tests decreased slightly, but with no change in ophthalmic reaction, there was no improvement. For this group, the titer levels were respectively 50, 100 to 250, 250, 250, 500 and 500 to 1,000. Since the titer levels are of the same order in both groups, no apparent relationship can be said to exist. In one patient serial dilution skin tests were not done, and his results are not with either group.

From this small group of fourteen patients suffering from hay fever and bronchial asthma, and studied intensively over a period of several years, the following tentative conclusions can be drawn regarding oral pollen therapy.

In all, an unexpected apparent blocking antibody response occurred. This level was not apparently related to the patient's clinical progress, since it was not consistently high in those who improved, or low in those who were worse.

In seven patients there was an unexpected decrease in skin test sensitivity, and in an eighth, an apparent reversal of the skin tests. In two subjects, there was a decrease in ophthalmic sensitivity.

In those patients in whom no ophthalmic test was present and the skin test sensitivity apparently decreased, there was marked improvement. In two patients in whom ophthalmic tests were present, and both they and the skin test decreased, one reported improvement and the other none. When the ophthalmic test was present and remained unchanged, no improvement occurred.

In the five patients in whom ophthalmic tests were present, and both they and the skin tests remained at the same level, no improvement, of course, was seen. In other words, with two exceptions, in the patients who gave no positive conjunctival tests, or in whom the skin and conjunctival tests decreased, there was improvement following oral pollen treatment. In those in whom conjunctival tests were present and remained unchanged, improvement did not occur.

A four-year follow-up of the remaining patients gave no significant long-range variations. One patient reported that he was still well, and others of the group took injection treatment with good effects.

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ORAL POLLEN THERAPY: A COMPARATIVE STUDY

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ATTEMPTS to desensitize hay-fever patients by the use of oral antigen have been described by several observers. Touart,[25] in 1921, reported the relief of symptoms following the oral administration of 1/10 mg. daily doses of pollen. Thommen[24] later showed the variability in absorption and the need for larger doses when the antigen was given by this route. Black, in 1927 and 1928,[3,4] reported 150 cases in whom a 1/20 solution of antigen had been administered orally. He demonstrated the pollen factor in the blood, urine and stools, and pointed out the variability of absorption when the antigen was administered by mouth. Gatterdam,[11] in 1933 and 1934, told of the use of a pollen solution in preseasonal, coseasonal and symptomatic treatment, with fair results, and emphasized the difficulty in adjusting dosage.

Stier and Hollister,[20] in 1937, treated a large series of cases with oral pollen extract in various solutions, with a reported 79 per cent satisfactory results. McGrew,[16] in 1937, used a 1 per cent extract, while Rockwell,[17] in 1938, employed whole dried pollen antigen. Bohner[6] has reported a comparative series of oral pollen and parenterally administered pollen with comparable results. Bernstein[2] and Kirsner pointed out that though peptic digestion does not destroy the pollen antigen, yet the immediate absorption through the intestine is slight. Bernstein and Feinberg,[2] using a ragweed pollen extract, found it necessary to use 450 times as much orally as parenterally. They also estimated that the immediate absorption into the blood stream was only 1/4,000 of that following hypodermic injection.

During the past ten years conflicting statements and opinions as to effectiveness of oral pollen therapy have been published, with Zeller[27] condemning its use as a method of self-medication, and emphasizing the severe reaction attendant on its use. London,[15] however, held that patients who had severe reactions to parenteral injection never had any reaction to doses of pollen by mouth and that therefore the antigen was not absorbed. The latter also stated that combined oral and parenteral therapy gave no better or worse results than injection alone. Black,[5] about the same time, published an opposite opinion. Alperstein[1] is satisfied that enteral absorption occurs and found both reagin and allergin in blood of orally treated patients, but thinks the oral method of treatment less effective than the administration by injection. Swartz[21] however,

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TABLE I. ANALYSIS OF THERAPEUTIC RESULTS
1937–1938

A				B				C			
Pollen Orally				Pollen Parenterally				No Pollen			
Good	Fair	Questionable	None	Good	Fair	Questionable	None	Good	Fair	Questionable	None
6	3	1	1	5	4	1	0	0	0	3	7

feels that oral therapy is equally as effective as injection treatment. Feinberg, et al[10] have published conflicting reports.

At the present time nearly all workers appear to agree that pollen is absorbed enterally. It is also agreed that the rate and nature of this absorption are variable. This study is an attempt to evaluate critically, from a clinical point of view, the results of a method of oral pollen therapy.

Our interest in the use of oral antigens was aroused by the statements of patients that they were relieved from spring hay-fever symptoms by eating honey, or from the symptoms of ragweed hay fever by eating ragweed leaves. Because of this and because of the confusion over the relative absorption of antigen given orally as compared with that given parenterally we have given oral antigen to a small series of patients who have suffered from ragweed hay fever. At first, in 1936, we gave dried ragweed leaf powder in capsules. We were not satisfied with the use of leaf preparations in the experiment because of the difficulty of achieving adequate dosage and of the lack of definite relationship between the atopen in the leaf and in the pollen. Therefore, pure pollen preparations were used in 1937, 1938, 1939 and 1940. These consisted of capsules containing increasing doses of the mixed dried pollens of the spring and of the fall type. Some of this we made up, though most of it was furnished to us by the Eli Lilly Company.

Those patients who had asthma were omitted from this series the first two years because of the uncertainty of the results of the treatment. We also omitted those who had been treated previously by the subcutaneous method for more than one season, because of the possibility of residual benefits from previous therapy. All other patients were taken in rotation and placed in one of the following three groups:

Group A. These patients received oral pollen and a placebo of Coca's fluid, subcutaneously.

Group B. These patients received an oral placebo exactly similar in appearance to the capsule containing the oral pollens and a routine pollen extract, subcutaneously.

Group C. These patients received an oral placebo and Coca's fluid, subcutaneously.

TABLE II. ANALYSIS OF THERAPEUTIC RESULTS
1938–1940

A				B			
Pollen Orally				Pollen Parenterally			
Good	Fair	Question-able	None	Good	Fair	Question-able	None
71	26	7	12	69	19	8	5

The groupings of all patients were changed each year; i.e., patients in Group A the first year who returned the second year were divided between Group B and Group C.

Results of therapy of all patients receiving adequate treatment and follow-up during the first two years of the study are shown in Table I.

The encouraging results of the first two years and the small number of patients studied prompted us to continue the work. During these years (1938 through 1940), only two groups were studied—Group A, receiving oral therapy; Group B, receiving parenteral therapy. The results of this study are shown in Table II, and the percentage interpretation of groups A and B of Tables I plus II are shown in Table III. Results were classified as *good, fair, questionable* and *none*. Patients were considered to have good results if they had less than a week's hay-fever or a very mild hay-fever during the mornings only for one or two weeks. They were considered to have fair results if they had a loss of the major symptoms and relief at night, and the season shortened by 50 per cent. They were considered to have questionable results if the patients themselves thought there had been improvement in spite of a continuation of symptoms. They were considered to have no results if neither patient nor doctor thought there had been improvement.

DISCUSSION

Maximum doses of 90,000 units were chosen arbitrarily the first two years. Some of our patients, however, received as much as 240,000 units every day while most were carried on 60,000 units twice a week. One of our patients on five different occasions developed asthma within two hours of taking 400 units by mouth while a dose of 200 units was well tolerated. Three patients developed general reaction with 15,000 units and were carried on a somewhat smaller dose. Several patients found the capsules mildly laxative. In six instances patients complained of abdominal pain of short duration within four hours of taking capsules. One patient not included in the series and previously treated for three years by the parenteral route with poor results, achieved 100 per cent relief with oral therapy used in connection with injections. In three cases combined oral and parenteral therapy increased the tolerated parenteral dose, and good results were obtained.

TABLE III. PERCENTAGE INTERPRETATION OF RESULTS
GROUPS A AND B OF TABLES I AND II

Combined Groups A					Combined Groups B				
Pollen Orally					Pollen Parenterally				
Good	Fair	Question-able	None	Total Cases	Good	Fair	Question-able	None	Total Cases
77	29	8	13	127	74	23	9	5	111
60.6%	22.8%	6.3%	10.2%		66.6%	20.7%	8.1%	4.5%	

In our experience oral therapy presents the *disadvantages* of:

1. Greater cost of material. However, a shorter preseasonal treatment is needed and thus fewer visits are required.

2. Variability of dosage and difficulty of control do demand more time and care per visit on the part of the physician. No rigid plan of dosage is completely satisfactory and since dosage must be based mainly on subjective evidence, great care must be used in interviewing the patient. We have come to feel that there is considerable individual variability in absorption. Certainly, the conflicting reports in the literature of attempts to demonstrate the enteral absorption of pollen antigen bear this out.

3. Results in our hands are slightly less satisfactory than those achieved by parenteral injection.

There appear, however, certain *advantages*:

1. Absence of severe reaction and ease of administration. For patients who have had, and fear, severe reactions, or for those in whom fear of a "needle" is highly developed, these features are welcome.

2. The treatment also is more readily available, and for patients who must travel as well as for the large group of vacationists, oral therapy offers a happy solution. Great care must be exercised in training such patients to use the treatment intelligently so that both safety and good results are obtained. Some of the poorer results in our group of cases are in those patients who were given a supply of capsules and then for some reason were not seen for too long an interval.

3. Desensitization can be achieved in most cases much more rapidly by the oral method and it is certainly the method of choice for those patients presenting themselves shortly before their season starts.

4. Highly satisfactory results can be achieved with oral pollen therapy, when it is carefully administered.

CONCLUSION

1. Oral pollen therapy offers a satisfactory method of treatment of seasonal hay fever.
2. It requires careful administration and management, and is in no sense a satisfactory self-directed treatment.

3. Oral therapy has definite advantages of administration and convenience which make it the method of choice in treating some patients who have seasonal hay fever.

ADDENDUM

Since the completion of this study one of us (J. M. P.) has had occasion to use oral pollen in:

1. Eight cases previously treated unsuccessfully parenterally; with success in four patients.
2. Fifteen cases where because of travel, injections were impractical; with success in eleven patients.
3. Five cases in conjunction with parenteral administration where previous injection treatment alone was unsatisfactory; with four successful cases.

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BENADRYL

A Clinical Evaluation Based on One Hundred and Seventy-one Case Studies

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BENADRYL, chemically known as Beta Dimethylaminoethyl Benzhydryl Ether Hydrochloride, was claimed to be a new antihistamine preparation which was synthesized and studied in the laboratories of Parke, Davis and Company.[4,5]

This drug was assigned to the Lancaster General Hospital for prelinimary clinical investigation on October 2, 1945.* Pharmacologically, the drug was claimed to have the ability to neutralize or counteract the effects of histamine. Experiments conducted on animals revealed that benadryl is fifteen to twenty times more active than aminophyllin experimentally in relieving bronchial constriction caused by histamine injection.[4,5]

The effect of benadryl was compared to that of papaverine. It was found to be 650 times as effective in antagonizing histamine; fifty times as effective in antagonizing acetylcholine.[3,4] Most investigators now agree that benadryl exerts a threefold action; first, an antihistamine action; second, an antispasmodic action; and third, an atropine-like effect.[3,4] This study has also convinced the author that the drug has a fourth effect, that of central nervous system depression.

Horton[6] has long been of the opinion that a common denominator exists in all allergic diseases (such as hay fever, asthma, urticaria, angioneurotic edema, migraine, et cetera) and also in some diseases that at the present time are not classified as allergic in origin. He states that the common denominator is edema which is provoked by the release of histamine or a histamine-like substance into the blood. The response produced by the release of histamine or the histamine-like substance can be either general or local.

Our assigned problem was to evaluate clinically the effect of benadryl on patients suffering from long-standing, recurrent, intractable asthma, chronic urticaria, recurrent migraine and any other conditions thought to be allergic in origin. If the etiology in all of the above-mentioned states is common, then treatment with a drug which has an antihistamine action could be easily evaluated.

This study covers a total of 171 cases. Similar cases are grouped as follows:

1. (a) Hay fever—32 cases. No previous treatment.
   (b) Hay fever—44 cases. Previously treated with specific pollen antigens.

*Benadryl was donated through the courtesy of Mr. Owen J. Rowlands of Parke, Davis and Company.

2. Intractable asthma, severe—21 cases.
3. (a) Chronic urticaria—21 cases.
   (b) Acute urticaria—28 cases.
4. Migraine—3 cases.
5. Atopic dermatitis—7 cases.
6. Erythema nodosum—1 case.
7. Perennial vasomotor rhinitis—11 cases.
8. Sea or motion sickness—2 cases.
9. Dysmenorrhea—1 case.

1. (a) *Hay fever—32 cases, no previous treatment.*—These patients all had typical symptoms, such as epiphora, lacrymation, sneezing, itching of the nose, rhinorrhea, congestion of the nasal mucous membrane accompanied by blocking, itching of the palate, coughing, et cetera. None of these patients had had previous desensitization therapy. The average dose of benadryl administered was 250 mg. per day, by the oral route. Six of this group of patients were completely relieved by the drug. These patients could not be classified as severe hay-fever sufferers. Twenty-six were relieved from 30 to 55 per cent. The amount of relief that they obtained was directly related to the pollen count. If the count was high, the patients' symptoms were more severe. A number of these patients experienced side reactions consisting of mild nausea, occasional vomiting, dizziness, generalized tingling, drowsiness, extreme in some cases, and a mild feeling of weakness. A number of these patients voluntarily increased the amount of benadryl they were taking as the severity of their symptoms increased. The side reactions were probably precipitated by the increased dosage. Five patients also complained of dryness of the mouth and mild difficulty in swallowing. In the six patients who received complete relief and in the twenty-six patients who received from 30 to 55 per cent relief, the dosage of the drug was gradually reduced to determine the minimum effective level of the drug necessary for relief. The amount of benadryl taken orally in the last-mentioned two groups was cut to between 125 mg. and 200 mg. daily. This was accomplished by giving each patient 25 mg. and 50 mg. capsules, with instructions to take 25 mg. q.i.d., if their symptoms were not severe, and 50 mg. q.i.d., if their symptoms were severe.

1. (b) *Hay fever—44 cases. Previously treated with specific pollen antigens.*—In this group of patients benadryl was used as an adjuvant. The patients were specifically instructed not to take the drug unless symptoms of hay fever were present. During the past fall, the pollen count in this area was extremely heavy between September 8 and September 24, 1946. Nineteen of this group of forty-four patients used benadryl during this period of time to provide symptomatic relief. Small doses of benadryl relieved most of these people. The average dose ranged between 25 mg.

t.i.d. and 50 mg. t.i.d. A number of other patients also seemed to tolerate pollen therapy much better. In this group of patients specific desensitization treatment plus benadryl when necessary to relieve symptoms when present provided relief in from 70 to 85 per cent of the cases.

2. *Intractable asthma, severe—21 cases.*—From 100 mg. to 400 mg. of the drug was used per day by means of the oral route. Fourteen (two-thirds) of these patients obtained no relief from the drug after taking the medication for three days or more. Five patients were definitely made worse by the drug. Two experienced hallucinations and extreme drowsiness after taking between 300 mg. and 400 mg. of the drug orally for a period of five days. On these two patients other methods of therapy were tried. The severe attack from which one of these patients was suffering, was finally relieved by the use of 7½ gr. aminophyllin in 50 c.c. of glucose every four hours intravenously. Oxygen and helium were also used on this patient, along with mechanical aspiration of the mucus that accumulated in the mouth and throat. No form of epinephrine was effective. This was also observed in other patients. The probability exists that benadryl may in some way counteract or neutralize the effect of epinephrine. The other patient's attack was not relieved by any form of therapy used. He died suddenly from what was thought to be a respiratory failure. It was found at postmortem examination that he had a pulmonary emphysema and hypertrophy and dilatation of his right auricle and ventricle. The examination revealed a chronic bronchitis, pneumonitis, pleuritis, fibrosis and pleural adhesions, and a slight nephrosclerosis of the arteriole type. There was no evidence of any acute or chronic degenerative changes that may have resulted from the ingestion of benadryl.

Another one of this group of five patients also died. Postmortem examination* revealed hypertrophy of the right auricle and ventricle. There was marked pulmonary edema, bilateral bronchopneumonia and a thrombosis of one of the pulmonary vessels with multiple small infarcts and passive congestion of the liver. The terminal portion of the duodenum showed central necrosis and erosion. There was no evidence of any toxic degeneration of the organs which may have been caused by the ingestion of benadryl.

Seven patients (one-third) derived some improvement following the ingestion of benadryl. Their attacks were less, more infrequent and they were more relaxed and slept better. Some of the patients in this group thought they were receiving sedation. Two of the patients compared the action of benadryl to that of triple bromides.

3. (a) *Chronic urticaria—21 cases.*—Here the results were excellent. The typical urticarial lesions would disappear shortly after preliminary in-

*Postmortem examinations performed by Dr. Thelma Boughton, Pathologist, Lancaster General Hospital, Lancaster, Pa.

gestion of from 50 mg. to 100 mg. of the drug. The average dose necessary to keep the patient free from lesions ranged from 25 mg. q.i.d. to 50 mg. q.i.d. It is well known that chronic urticaria has long been a troublesome problem and still remains so. The itching, insomnia, pain, nervousness and other symptoms that accompany chronic urticaria are quite annoying. The condition at times is very dangerous if localized edema occurs in the larynx, trachea or pharynx. Many forms of therapy have been employed to give these sufferers even short periods of freedom from symptoms. The relief obtained by these patients following benadryl therapy was so striking and complete that the drug will probably be the one of choice in the treatment of chronic urticaria in the future. This statement is made in spite of the fact that a large number of patients experienced drowsiness after the ingestion of the drug. Three of the patients in this group also complained of inability to concentrate and co-ordinate properly after taking the drug over a period of time. Prompt recurrence of the urticaria took place in practically the entire group of patients when benadryl was temporarily discontinued.

Therefore, diagnostically, the physician must try to determine the etiology of the urticaria. This sometimes can be accomplished by skin testing or by careful history taking; however, if the specific reagins are absent in the blood stream, skin tests give the investigator no information. Curtis and Owens[1] first reported the use of benadryl in the treatment of acute and chronic urticaria. Later P. A. O'Leary and E. M. Farber[7] also published a paper on the same subject. Their reports were enthusiastic.

3. (b) *Acute urticaria—28 cases.*—Nineteen of these patients experienced almost immediate relief after benadryl therapy was instituted. The itching and nervousness from which they suffered usually disappeared about four hours after benadryl therapy was begun. Five of this group of patients also improved, even though their lesions did not completely disappear. It was necessary to discontinue the use of benadryl in the remaining four members of this group because of the appearance of extremely severe, so-called, side chain reactions, consisting of nausea, dizziness, blurring of vision and extreme drowsiness.

4. *Migraine—3 cases.*—None of these patients obtained any relief following treatment with benadryl. One patient, a sufferer of long standing, then decided to take 150 mg. of the drug as soon as his symptoms started. He obtained no relief, even though he repeated the dose several times after his symptoms appeared. He developed side reactions such as vomiting, dizziness, dryness of tongue, difficulty in swallowing and some blurring of vision.

5. *Atopic dermititis—7 cases.*—All members of this group of patients were less than six years old. The dose of benadryl ranged from 12½ mg.

q.i.d. to 25 mg. q.i.d. and the average duration of therapy was eleven days. There was some slight improvement in two of the cases. I attribute this improvement to a diminution of the itch reflex. None of the cases cleared.

6. *Erythema nodosum—1 case.*—This patient was given 50 mg. of the drug four times daily. He experienced no relief after taking the drug for a period of four days. He also experienced no side reactions.

7. *Perennial vasomotor rhinitis—11 cases.*—Nasal discharge, sneeze reflex, itching of the nose were all reduced in seven of this group. The other four patients received no relief from the drug. The dose of benadryl used ranged from 25 mg. q.i.d. to 50 mg. every four hours. Seven patients obtained relief from the ingestion of the drug. They immediately experienced remissions if they discontinued its use.

8. *Sea or motion sickness—2 cases.*—The author was one subject and a fellow physician was the other. Neither of us obtained relief. The author experienced extremely severe side reactions such as nausea, dizziness, vomiting, tingling and blurring of vision. However, in all fairness, it must be stated that movement of the boat was probably responsible for many of these symptoms, and this report is by no means conclusive.

9. *Dysmenorrhea—1 case.*—This patient took 50 mg. of the drug every four hours for a period of three days without relief. In studying this group of patients, the author noticed that the two most frequent side reactions were nausea and drowsiness. All of us occasionally have to deal with troublesome insomniacs. Benadryl was used by one such patient. He was instructed to take 100 mg. of the drug at 4:00 p.m. and another 100 mg. at 8:00 p.m. He experienced complete relaxation for the first time in several years and was able to obtain a complete night's rest. This patient is also more relaxed during the day and is able to do his work in a more efficient manner. This experience has further convinced the author that benadryl has a depressant effect on the central nervous system. Further trial in conditions of this kind is indicated.

CONCLUSION

1. Loew and his associates had tested the toxicity of benadryl in rats and guinea pigs and found it to be low.
2. Curtis and Owens first used the drug on human beings. They noticed the drug had a wide margin of safety.
3. Benadryl is a very useful addition to our therapeutic armamentarium, especially in the following conditions: acute and chronic urticaria, hay fever, and perennial vasomotor rhinitis. It is also of limited value in some cases of intractable asthma.
4. The extent and method by which the drug interferes or neutralizes histamine is still not known. Further study is indicated.

5. The drug very definitely seems to have a sedative effect. Benadryl seems to counteract and neutralize the effect of adrenalin or epinephrine. Benadryl very definitely does not relieve the majority of asthmatics studied; it proved of no value in the treatment of migraine, seasickness, dysmenorrhea, and one case of erythema nodosum. It proved of little value in the treatment of atopic eczema.

6. Careful allergy studies should be conducted on all allergic persons to determine the etiology of the condition from which the patient is suffering. Elimination of the cause or focus of infection and careful desensitization treatment, if indicated, is still the best procedure. Benadryl can be used to provide symptomatic relief in those conditions in which it is effective. It should not be used indiscriminately, as it produces serious side reactions.

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ASTHMA IN THE NEWBORN

In the July-August issue of the *Hawaiian Medical Journal,* F. D. Nance reports seven cases, which came under his observation and which illustrate the following points.

1. Asthma in the newborn is not uncommon, but is probably the most frequent cause of a wheeze in these infants.

2. It is almost always dietary in origin.

3. Since the diet at this age is extremely limited, the detection of the offending food is simple.

The author concludes that the history that an infant wheezed since birth plus the finding of an expiratory wheeze should suggest a probable diagnosis of asthma due to food allergy. Physicians should be unwilling to accept a diagnosis of thymus enlargement as the cause of noisy respiration in the newborn on the basis of roentgen observations alone.

KAPOSI'S VARICELLIFORM ERUPTION

Relation to Atopic Dermatitis

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DEFINITION: Kaposi's varicelliform eruption is a rather rare condition which is now acceptable as a distinct disease entity. It is characterized by a stormy onset with high fever, prostration, nausea, vomiting, diarrhea, and signs of kidney irritation. The rash is almost entirely localized to parts of the skin previously affected by a chronic dermatitis, usually allergic or atopic; vesicles and pustules with umbilication are typical.

CASE REPORT

Miss N. J., aged nineteen years, a school teacher, was admitted to Wesley Memorial Hospital at 3:00 A.M., September 4, 1944, acutely ill, with high fever. She developed a sore throat five days previously, and a physician prescribed a sulfa tablet every three hours. A papular rash began on the body and spread to the arms, face, neck and upper part of the back. The drug was stopped after two days. Fever, prostration, nausea, vomiting, bloody diarrhea, and hematuria soon followed, and the eruption spread rapidly and became vesicular. Pruritis was not a complaint. The temperature was 104° F. the day before admission.

She had been under treatment by another physician for about eight or nine years for hay fever and severe flexural "eczema" (atopic dermatitis), especially affecting the bends of the elbows and sides of the neck. She had been found allergic to many foods and pollens. The previous history was otherwise not noteworthy. She had an old vaccination scar.

Examination.—She was a well-nourished white woman with the deeply pigmented, hyperkeratotic skin of her neck swollen and oozing, and with many unbroken vesicles, most of which were umbilicated. Lesions were also present on the face, neck, arms, upper chest, and in the groins. The palms, soles and mucous membranes were not involved. The individual lesions were from 5 to 7 mm. in diameter, thick walled, and pearly in appearance. There was no surrounding erythematous aerola or scratch marks. New lesions appeared for several days. Much pain occurred in turning the head from side to side (Fig. 1).

Stupor was present on admission, and the fever reached 105° F., with a pulse rate of 126 on September 6, two days after admission and seven days after the onset of illness. Delirium and involuntary urination occurred, and the temperature remained high for two more days; it then returned to normal rather rapidly (Fig. 2). The entire duration of fever was about eleven days. As the fever began to recede, the mental condition improved, as well as the general appearance, and the rash began to fade. At the time of discharge, September 17, the vesicles were gone, the skin was stained, without scars, but the previously lichenified flexural dermatitis was still present.

Physical examination was otherwise practically normal. The pharynx was red; no pulmonary, cardiac, abdominal nor pelvic abnormalities were found.

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The author acknowledges, with gratitude, the aid of Arthur William Stillians, M.D., and Michael Higgins Ebert, M.D.

Laboratory findings.—The urine, of which only 2,250 c.c. were excreted one day despite an oral and intravenous intake of 4,950 c.c., contained 50 to 100 mg. of albumin per 100 cubic centimeters, but no blood nor casts. The blood contained 4,080,000 red cells with some anisocytosis and polychromasia, 13 grams (83 per cent)

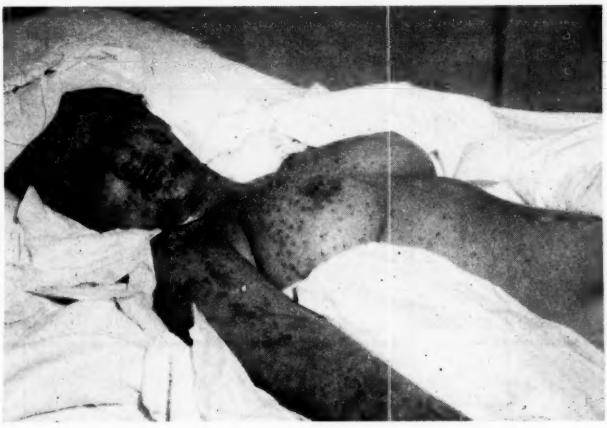

Fig. 1. N. J., aged nineteen years, with marked umbilicated vesiculopustular eruption superimposed on sites of previous atopic dermatitis; high fever and prostration associated.

of hemoglobin, and 11,400 and 11,850 white corpuscles, of which 88 per cent were polymorphonuclear leukocytes, 10 per cent lymphocytes, 1 per cent basophiles, and 1 per cent monocytes. Despite the underlying allergic condition, eosinophiles were not found (a common occurrence in allergic individuals who suffer from some superimposed, nonallergic disease). Toxic granulation of the neutrophiles was found. The Kahn and Wassermann tests were negative; the carbon dioxide combining power was 34.9 volumes per cent; the serum total protein was 5.31, with albumin 3.1 and globulin 2.21. Culture of the blood gave no growth, but culture of the contents of a vesicle yielded a heavy growth of hemolytic Staphylococcus albus. No parasites were found in the feces.

The local treatment consisted of cool dressings of 6 per cent aluminum subacetate solution until the fever disappeared; then an ointment of borated petrolatum, 10 per cent. A boric acid lotion was used to irrigate the conjunctival sacs. The treatment was otherwise symptomatic, with main emphasis on large intake of fluid, much of which was administered intravenously.

At first there was some doubt as to the diagnosis, chiefly because of the possibility of a sulfonamide reaction, but the correct diagnosis was suggested by Dr. Stillians, consultant.

Dr. Ebert isolated the virus of herpes simplex from one of the vesicles by injecting the material into a rabbit's cornea, but lost the virus in transmission experiments.

ETIOLOGY OF KAPOSI'S VARICELLIFORM ERUPTION

In 1887 Kaposi[19] described a new disease which was an alarming complication of "eczema infantum." The vesicles were described as lentil-sized, "filled with a clear serum, and the majority umbilicated." Kaposi

called this eruption "varicelliform," but stated that the term "eczema herpetiforme" is also correct.

Since this work there has been a controversy among dermatologists

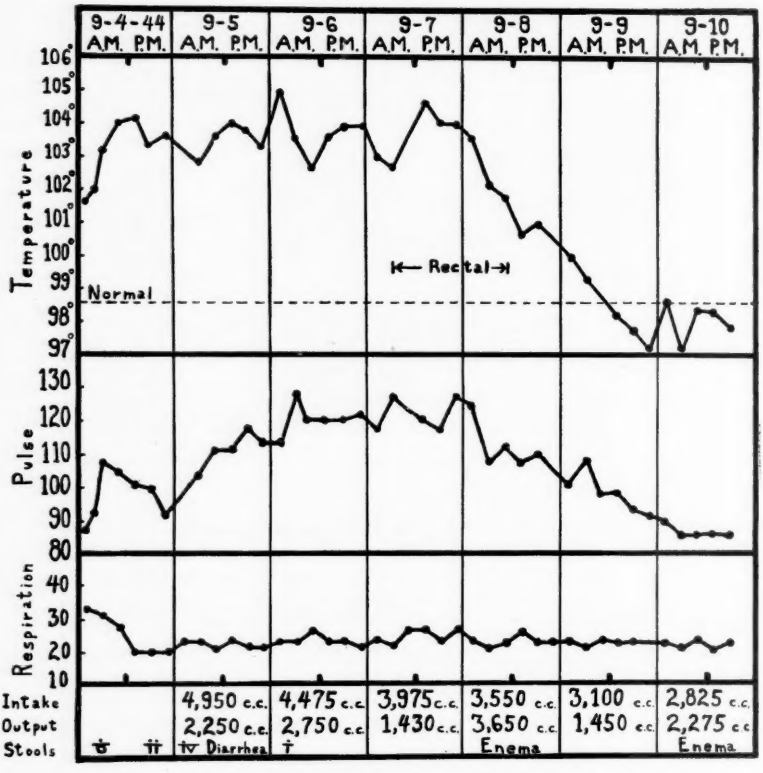

Fig. 2. Temperature, pulse and other data during height of attack.

concerning the relation of this disease to vaccinia accidentally superimposed on infantile eczema. Both occur only upon already inflamed skin, and both have lesions resembling those of smallpox (variola). This controversy has now been settled by the discovery of Seidenberg,[28] who showed that the virus of herpes simplex is the causative agent of Kaposi's varicelliform eruption and that it has no relation to vaccinia.

This discovery has been amply verified by Wenner,[31] Heilman in a case reported by Barton and Brunsting,[1] Blattner and Heys, reported by Lane and Herold,[21] and by Lynch and co-workers.[22] Further confirmation comes from the recent article by Blattner, Heys, and Harrison.[5] These authors isolated a filterable virus of the herpes group from fluid removed from cutaneous vesicles on the fifth and sixth days of illness. The patient

was a fifteen-month-old white baby boy who had had atopic eczema since the age of six weeks and who then developed an acute exanthem, with high fever and leukopenia. The patient recovered and left the hospital in fourteen days; the acute lesions completely disappeared, and the infantile eczema was less marked than it had been for a long time. "The virus was isolated not only by means of the rabbit's cornea but also directly on the chorioallantois of the developing hen's egg. The latter finding would seem to exclude any possibility that a latent herpes virus might have been reinactivated in the rabbit by experimental manipulation." Kaposi's varicelliform eruption is therefore almost certainly due to a virus of the herpes simplex group; it is not related to vaccinia.

Lynch[22] points out the difficulty in isolating the virus, which must be sought from unruptured vesicles, "preferably not over one or two days old. For these reasons it is likely that the diagnosis of herpetic complication of eczema will usually be made on a clinical basis. The pathogenesis seems to be well established, and it is now only necessary for clinicians to become familiar with the disease."

Staphylococci and streptococci have been isolated by many observers (we isolated hemolytic Staphylococcus albus). But these bacteria are apparently secondary invaders.

Other articles concern this condition and the heretofore confusing vaccinia superimposed on eczema. Some of the authors are Juliusberg,[18] Ellis,[11] Corson and Ludy,[10] Goeckerman and Wilhelm,[16] MacLachlan and Gillespie,[23] Tedder,[30] Schwartz,[27] King,[20] Ronchese,[26] Brown,[8] Freud,[12] Freund,[13] Frühwald,[14] Bentley,[2] Platou,[25] Brain and Lewis,[7] Strickler,[29] Blattner, Heys and Harrison,[4], Blattner, Heys and Gollub,[3] Hershey and Smith,[17] Connor and Gonce,[9] Wise and Sulzberger,[32] and Pepple, Murrell and Fowlkes.[24]

The *incidence* of the disease seems to be on the increase. At least thirteen cases have been listed from the Mississippi Valley region within the past three years. The total number of cases is unknown as many are not reported, but probably almost a hundred have occurred.

Predisposing cause.—Almost every case has occurred in a patient who already had a skin disease. Of sixty-seven cases reported by Barton and Brunsting[1] in 1944, fifty-three (79 per cent) had atopic dermatitis (allergic eczema, neurodermatitis). This high percentage is very important to allergists and dermatologists as it indicates the danger which may befall patients with "eczema" from contact with a virus disease such as herpes simplex. Seborrheic dermatitis occurred in thirteen patients, and impetigo in thirteen patients. Scabies, sycosis vulgaris, and simple trauma may also precede the varicelliform eruption. Of the fifty patients for whom the sex was listed, thirty were males, twenty females. Children three years old or younger were affected in fifty-one of these sixty-seven cases, with only thirteen patients over fourteen years of age. Small epi-

demics have occurred, as Kaposi[19] saw ten cases within a short period, and McLachlan and Gillespie[23] found sixteen cases in a British hospital for children. These groups suggest that an increase of virulence of the virus occurs at times.

SYMPTOMATOLOGY AND DIAGNOSIS

The main findings are sudden onset with prostration, fever, nausea, vomiting, diarrhea, and the typical rash, as already mentioned. The onset is usually sudden with a quick rise in temperature to 103° to 105°; the temperature usually remains high for several days, then drops by lysis. The pulse is rapid with the fever. Prostration and stupor are common, as in our case, and delirium and mental confusion are frequent. Death may follow.

The rash itself is typical. Many of the lesions are umbilicated vesicles which become pustular, with new lesions appearing for several days. They heal with little or no scarring. The lesions usually appear on skin which is already affected by some form of dermatitis, especially that of the atopic type. Regional lymphadenitis is also present, especially cervical.

Complications have been noted, e.g., anuria, otitis media, purulent rhinitis, conjunctivitis, and occasionally severe infections of the regional lymph nodes. Involvement of the mucous membranes is uncommon.

Moderate increase in leukocytes is usual. Albumin and casts may occur in the urine, and melena is not uncommon.

The finding of the herpes-like virus confirms the diagnosis, but the clinical findings themselves are diagnostic.

DIFFERENTIAL DIAGNOSIS

Other conditions in which vesicles and pustules occur and all causes of prostration and fever must be ruled out. Variola, eczema vaccinatum, varicella, drug eruptions, impetigo, herpes zoster, and secondary pyogenic infection in a patient with eczema are especially important.

From *variola* the disease can be distinguished by the absence of a prodromal period of about three days, the failure of the symptoms and fever to subside on appearance of the eruption and to recur about the eighth day, and the recurrence of vesicles for a week or ten days. Variola also tends to involve the hands and soles, a finding usually absent in Kaposi's condition. The presence of a good vaccination mark in a severe case previously afflicted with chronic dermatitis also speaks against the diagnosis of variola.

The differentiation from *eczema vaccinatum,* vaccinia inoculated upon a pre-existing dermatitis, is difficult. A history of exposure to cowpox vaccine and the absence of a vaccination scar favor the diagnosis of vaccinia, but this condition usually spreads rapidly over most of the body. Kaposi's varicelliform eruption, on the other hand, usually symmetrically involves the upper half of the body. Identification of the virus may be

necessary before a decision can be reached; as already pointed out the viruses of the two conditions are not related. Vaccinia is a serious condition with a high mortality. Vaccination of persons with dermatitis is extremely dangerous, and patients with dermatitis must avoid recently vaccinated individuals and vaccinia unless they themselves have been immunized by previous vaccination. Glaser[15] has seen at least six cases of eczema vaccinatum.

From *varicella* all except the mildest examples of Kaposi's eruption are distinguished by the frequent involvement of the face, the tendency to confluence of the eruption upon pre-existing areas of dermatitis, especially the sides of the neck, and the stormy onset and course.

Drug eruptions may confuse. In this case, sensitization to sulfonamide drug was at first suspected because the condition occurred very quickly after the drug was administered. But drug rashes are not restricted to pre-existing areas of dermatitis, nor do they exhibit the typical umbilicated type of eruption. The clinical course is also different.

In *impetigo* the variation in the size of the lesions, their fragility, asymmetry, and lack of definite and regular umbilication distinguish it from the varicelliform eruption. Impetigo is not self-limited, and seldom attacks with such ferocity except in young infants; leukocytosis usually accompanies these very rare severe episodes.

In *herpes zoster,* even in the rare disseminated form, there should be some unilateral predilection, with smaller groups of lesions, not often upon a previously inflamed skin. Pain often precedes the eruption, and fever is uncommon. The lesions are not definitely umbilicated.

Secondary pyogenic infections occasionally occur in eczema. Fever, leukocytosis and prostration may be severe in infants, but the characteristic thick-roofed vesiculo-pustular eruption does not occur. Boisveit and Powers[6] state that atopic dermatitis and streptococcal fever (rhinopharyngitis, cervical adenitis, low-grade fever of several weeks' duration) are common diseases in the first three years of life.

PROGNOSIS

The general practitioner, as well as the pediatrician, dermatologist, and allergist, should be on the lookout for this varicelliform eruption. It has a considerable mortality which, according to Barton and Brunsting,[1] amounts to 27 per cent in infants under three, and to more than 15 per cent in adults. One has only to see one case to realize the extreme prostration and danger.

TREATMENT

This may well be divided into *prophylactic* and *active;* the former is important. Individuals with eczema or other dermatological conditions should rigidly avoid virus conditions, especially simple cold sores (herpes simplex). A mother or nurse who has one of these virus diseases must

not contact infants and children who have a skin disease. The attending physician should point out these dangers. Allergists in particular should acquaint themselves with this disease.

Active treatment to date is chiefly symptomatic. Local measures vary. Cool dressings of 6 per cent aluminum subacetate solution may be applied while fever exists; borated petrolatum, 10 per cent, may then be used. The usual measures given for prostration and feverish conditions are necessary, especially fluids given orally, intravenously, subcutaneously, and/or rectally, as the emergency requires. Sulfonamide therapy has been praised by Connor and Gonce,[9] who obtained good results in two of their three patients, but Lane and Herold[21] observed a dangerous leukopenia in one case.

Lynch[22] has suggested that pooled serum or plasma of adults contains sufficient antibody to be of service in combating the effects of the virus of herpes simplex. This therapy may well be effective in the treatment of the varicelliform disease and eczema vaccinatum, both dangerous, both virus diseases, though not related.

SUMMARY AND CONCLUSIONS

1. Kaposi's varicelliform eruption occurred in a young woman with previous atopic dermatitis (eczema). Recovery occurred after a stormy course with prostration, high fever, and typical vesiculopustular umbilicated lesions.

2. The condition has been definitely proved to be due to a virus of the herpes simplex group which infects individuals with previous skin disease, especially atopic dermatitis.

3. The virus of the varicelliform condition is not related to that which causes eczema vaccinatum.

4. The etiology, symptomatology, diagnosis, differential diagnosis, prognosis, and treatment are outlined.

5. Physicians should warn individuals with eczema or other dermatological conditions to avoid persons who have herpes simplex because of the danger of developing Kaposi's varicelliform eruption.

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INSUFFLATION OF SULFONAMIDE DRUGS

"Sensitivity from Insufflation of Powdered Sulfonamide Compounds in Acute Infections of Nose and Throat" is the title of a paper by H. C. Ballenger, M.D., published in the July, 1947, issue of *Anesthesiology*.

Ballenger applied sulfathiazole, sulfanilamide and sulfadiazine powders, alone or in combination, by insufflation to the mucous membrane of the upper respiratory tract in 1,500 patients with various acute infections of the nose and throat. Six thousand applications were made during a three-year period from July 1, 1943 to July 1, 1946. An average of about 2.5 treatments were given for each acute attack. Many of the patients have had two, three or more attacks during the three-year period. The sore throat and inflammation, especially that of the palate, nasopharynx and pharynx, were frequently stopped within twenty-four hours. The rhinitis and

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MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

V. Further Studies with Mold Extracts

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A MAJOR activity of the Association of Allergists for Mycological Investigations continues to be the study of various methods of preparation of mold extracts. Reports[2,4] in 1944 described the preparation of four experimental extracts and the results of skin testing with these antigens. Pellicles of *Alternaria tenuis* and *Aspergillus niger* used in these studies were subjected to twenty washings with normal saline, then were modified further for extraction as follows:

Method 1—Dried only by lyophilization.
Method 2—Dried by lyophilization, defatted.
Method 3—Dried by lyophilization, defatted, ground.
Method 4—Dried by lyophilization, ground.
Method 5—"Usual Method" (dried slowly).

Intradermal skin tests with dilutions of 1:1,000 failed to elicit any significant difference between any of the experimental extracts and extracts prepared by our "usual method" (No. 5). In none of these extracts could histamine or a histamine-like substance be detected to account for any irritating properties which the extracts might possess.[6] It was, therefore, concluded that our acknowledged[1] lack of reliable extracts was based upon insufficient concentration of the active substance rather than upon nonspecific irritating properties. Finally, a study of the pellicle washings and of the broth in which the pellicles were grown revealed the presence of skin-reacting substances, not only in the broth but also in the washings, when tested on Alternaria-sensitive patients (5); this was correlated with an absence of histamine or histamine-like substance.[6]

EXPERIMENTAL EXTRACTS 6 TO 12

In order to continue the study of various methods of extraction, more extracts were prepared in the summer of 1944 from the same two molds, *Alternaria tenuis* and *Aspergillus niger*. The pellicles were separated as thoroughly as possible from the broth by decanting and filtration, cut into thin strips, and, without any washing, were frozen immediately between

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cakes of dry ice, then dried by lyophilization. A portion of the lyophilized pellicle was mixed in a Waring Blendor with Hollister-Stier solution in a ratio of 1:20 and, after extracting in the refrigerator for forty-two hours, was sterilized by Seitz filtration. Another portion of the lyophilized pellicle was defatted in Soxhlet equipment with ethyl ether, after which it was extracted similarly. The broth which had been freed of all pellicle and spores was lyophilized. This was accomplished easily with the Aspergillus broth, but with Alternaria broth a certain amount of gummy residue could not be avoided. The lyophilized broth was redissolved in Hollister-Stier solution in ratio of 1:10, based on the dried broth.

An effort was made by one of us (Tatge) to separate the protein molecule into large and small molecular aggregates by dialysis, in order to obtain a potent skin-reacting fraction that would produce specific whealing, lessen the incidence of nonspecific reaction, and cause no constitutional reaction when used intradermally for diagnosis only.

It had been shown by Johnson and Rappaport[8] that ragweed pollen extract could be split by dialysis into at least two fractions, the dialysate containing a highly skin-reactive aggregate and the semipermeable membrane retaining an antigenic fraction, possibly of lower skin reactivity.

On this basis, work was begun on *Alternaria tenuis* pellicle, *Alternaria tenuis* broth, *Aspergillus niger* pellicle, and *Aspergillus niger* broth. Pellicles and broth were separated and the unwashed pellicles were dried completely in an air-conditioned drier, then ground to a powder in the ball mill. The powdered pellicles were extracted in distilled water in 1:20 ratio and this extract dialysed in a cellophane bag against an equal volume of water for forty-eight hours. The dialysate labeled small aggregate and the bag contents labeled large aggregate were placed in evaporating dishes and concentrated in the drier with a continuous stream of warm air (80° F.). The residue of the small molecular fraction was gummy, but that of the large molecular fraction was drier and less gummy. Each fraction then was dissolved in Hollister-Stier solution in 1:20 ratio and sterilized by Seitz filtration. From the broths similar extracts were prepared.

With Alternaria, it was found that unless the cellophane bag was changed at the end of twenty-four hours it would disintegrate. Similar enzyme activity has been noted in other experiments involving Alternaria pellicle extract and broth, but it has not been observed with *Aspergillus niger.*

In order to minimize the influence of aging, all the extracts were prepared as nearly simultaneously as possible. These extracts were labeled only with serial numbers 6 to 12 and were distributed to our membership for skin testing. For comparison, an extract freshly prepared according to our "usual method" (5) was included. To recapitulate, these extracts were prepared as follows:

TABLE I

METHOD	ALTERNARIA TENUIS BC 17										ASPERGILLUS NIGER BC 70									
	Intradermal Tests								Scratch		Intradermal Tests								Scratch	
	1:100,000		1:10,000		1:1,000		1:100		1:20		1:100,000		1:10,000		1:1,000		1:100		1:20	
	Cases tested	Reactions	Cases tested	Reactions	Cases tested	Reactions	Cases tested	Reactions	Cases tested	Reactions	Cases tested	Reactions	Cases tested	Reactions	Cases tested	Reactions	Cases tested	Reactions	Cases tested	Reactions
"Usual" No. 5 Washed, slowly dried pellicles	19	6 32%	27	13 48%	29	20 69%	24	24 100%	18	7 39%	18	0	18	1 6%	18	2 11%	18	7 39%	17	3 18%
No. 6 Unwashed, lyophilized pellicles	18	5 28%	26	15 58%	29	22 76%	24	23 96%	18	5 28%	18	0	18	1 6%	18	2 11%	18	12 67%	17	4 24%
No. 7 Unwashed, lyophilized, defatted pellicles	18	5 28%	26	14 54%	29	22 76%	24	24 100%	18	5 28%	18	0	18	1 6%	18	4 22%	18	9 50%	17	3 18%
No. 8 Broth	19	10 53%	27	18 67%	29	25 86%	24	24 100%	18	9 50%	18	0	18	3 17%	18	6 33%	18	15 83%	17	2 12%

Members performing the studies from which above data taken:

Dr. Sam Sanders
Dr. Edw. George Tatge
Dr. F. W. Wittich
Dr. Homer E. Prince

Method 5—"Usual method" (washed, slowly dried pellicle).
Method 6—Unwashed pellicle, lyophilized.
Method 7—Unwashed pellicle, lyophilized, defatted.
Method 8—Broth.
Method 9—Unwashed pellicle, "small aggregate" (dialysate).
Method 10—Unwashed pellicle, "large aggregate" (bag contents).
Method 11—Broth, "small aggregate" (dialysate).
Method 12—Broth, "large aggregate" (bag contents).

The results of skin testing on twenty-nine patients are shown in Table I. In all the patients, molds were considered by the investigators to be major allergens; Alternaria was specified in twenty patients and implied in the remaining nine. On the other hand, *Aspergillus niger* was not specified once as a major allergen, even though the investigators also tested eighteen of the patients with this mold. In the tests with *Alternaria tenuis,* there did not seem to be any significant difference in the reactivity of preparations 5, 6, and 7, all of which were pellicle extracts. Therefore, the fact that the pellicles were washed before extracting by the "usual method" did not seem to have weakened the extract, when compared with extracts of unwashed pellicles. Furthermore, defatting the pellicles by method 7 did not result in a better extract. On the other hand, method 8, which was culture broth, appeared to be more reactive than any of the pellicle extracts, both by intradermal testing in dilution of 1:1,000, or greater, and by the scratch method. Similar differences were suggested from the tests with *Aspergillus niger,* although, as would be expected, the incidence of positive reactions was distinctly less with all dilutions.

When the results of skin testing with large and small aggregate extracts (methods 9, 10, 11, and 12) were presented in Pittsburgh in January, 1945, it was shown that there was very little difference in the reactivity between the large and small fraction extracts. Dr. George Rockwell pointed out that an equilibrium had been reached between the bag contents and the dialysate, and that Donnan's Law only had been fulfilled. This was obvious, though overlooked, since the cellophane bag had merely been changed and replaced in the original dialysate until a period of forty-eight hours had elapsed.

After the Pittsburgh meeting, methods 9, 10, 11, and 12 were repeated with *Alternaria tenuis* with the following modification: The bag contents were dialyzed against an equal volume of distilled water and the dialysate was removed for evaporation once every twenty-four hours, a quantity of distilled water equal to the measured bag contents being replaced for purpose of further dialyzation. It was found that after five days, or five changes of dialysate, practically no residue was left when the dialysate was evaporated to dryness in the drier. It was believed that all of the small aggregate had passed through the membrane. The five dried, gummy dialysates were added together, dissolved in Hollister-Stier solution in 1:20 ratio, and sterilized by Seitz filtration. The bag contents were

TABLE II

METHOD	ALTERNARIA TENUIS BC 17									
	Intradermal Tests								Scratch	
	1:100,000		1:10,000		1:1,000		1:100		1:20	
	Cases tested	Reactions	Cases tested	Reactions	Cases tested	Reactions	Cases tested	Reactions	Cases tested	Reactions
No. 9-B Unwashed pellicle Small aggregate (dialysate)	20	0	19	3 16%	29	5 17%	16	5 31%	10	0
No. 10-B Unwashed pellicle Large aggregate (bag contents)	30	17 57%	29	20 69%	37	26 70%	25	24 96%	10	2 20%
No. 11-B Broth Small aggregate (dialysate)	30	4 13%	31	1 3%	39	9 23%	26	10 38%	10	4 40%
No. 12-B Broth Large aggregate (bag contents)	30	18 60%	31	23 74%	38	26 68%	25	24 96%	10	3 30%

Members performing studies from which above data taken:

Dr. Wm. L. Marr
Dr. Ethan Allan Brown
Dr. L. Dell Henry
Dr. Erle D. Sellers
Dr. J. H. Black
Dr. Homer E. Prince

dried and extracted similarly. These extracts were denoted by numbers 9B, 10B, 11B, and 12B to distinguish them from those prepared in 1944. With certain other experimental extracts, they were distributed for skin testing late in 1945.

Although Alternaria-sensitive patients were available for experimental testing, the selection of persons clinically sensitive to *Aspergillus niger* was somewhat difficult. Therefore, in extract 9B and in all subsequent experimental extracts *Alternaria tenuis* only has been used.

Table II shows the results of skin testing with these extracts on Alternaria-sensitive patients. Although dialysis did not seem to separate Alternaria pellicle extract and Alternaria culture broth completely into skin-reactive and nonreactive fractions, a very definite tendency to retain skin-reactive fractions within the cellophane bag was observed. This failure to remove an aggregate of high skin reactivity from the bag contents was surprising. No explanation has been offered, unless it is on a basis of some peculiarity in the structure of the skin-reacting fraction of Alternaria extract. It has been suggested that the enzyme activity of Alternaria preparations may alter the permeability of cellophane sufficiently to interfere with dialysis.[7]

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MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

VI. Intrinsic Fungous Factors in Relation to Asthma

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THE use of the term "intrinsic" in the title of this paper in reality is not correct. Actually, I wish to emphasize the thought that a patient may be sensitized to fungi which have become an integral component of the bronchial flora and thus he is exposed to more or less constant contact with an allergen.

Over a period of years we have studied the sputum of patients with asthma, both microscopically and by culture. In a small percentage of patients, there has been found what appears to be an infestation of the bronchial secretions by nonpathogenic fungi of various kinds. Extracts of these fungi have given excellent positive scratch and intradermal reactions in some patients. Passive transfer has been obtained. Improvement in symptoms has followed hyposensitization.

By this means, a small but significant number of patients have been definitely benefited. A few such patients presented no other sensitizations or other factors to explain their asthma and for them results have been striking.

That, briefly, is the thesis of this paper and it is my opinion that it is worth while to consider such a possibility in patients who either fail to respond to more routine measures or in whose sputum fungi are exhibited on initial routine examination.

METHOD OF EXAMINATION

In our laboratory, routine study of the sputum consists of examining the usual stained smears for the character of the cells, the character of the usual flora, and tubercle bacillus. In addition, a fresh wet mount is examined by bright light for fungi and by darkfield for spiral organisms. Sometimes it is necessary to examine several specimens before representative findings are observed. If for any reason we suspect the presence of fungi, a spot plate is made on Sabaurand's or wort agar. This is done by selecting about 30 loopfuls of material and depositing them on the agar surface without streaking. The plates are sealed and incubated at room temperature for one to three weeks. If fungi which are cultivable by this method are present, colonies will develop from a varying number of the spot cultures. From such a culture one can get a fair gage of the intensity of the fungus infestation. Only rarely will all the spots develop colonies of fungi. The average specimen of significance

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will show positive spots in 25 per cent to 50 per cent of all spots cultured.

The patients, from whom such cultures are obtained, are subjected to careful examination to determine if the isolated organism is producing a mycosis *per se*. X-rays, blood studies, physical examination, et cetera, are made.

METHOD OF EXTRACTION

In each instance that positive fungus cultures are obtained, transfers are made into a broth culture of sufficient sugar concentration and correct pH to obtain heavy growth. As a rule, a dense mat of growth covers the surface of the medium within several days at room temperature. This is dislodged and pushed to the bottom of the flask and incubation continued. In a period of several weeks, four or five such mats are obtained in this manner in the same flask.

After sufficient growth is obtained, the flask is inverted and drained, the medium being carefully saved and filtered through a Seitz filter. To the remaining mats of fungus is added a sufficient amount of Coca's buffered saline to just cover the growth, usually 50 to 75 c.c. This mixture is allowed to extract for two days in the ice box and then filtered through a Seitz pad. A volume of glycerine equal to the filtrate volume is added and the finished product bottled. A few such extracts have been dialyzed and some have been concentrated by evaporation through a cellophane bag suspended in air. The latter have been used for experimental purposes. A bottle of the medium alone is kept on the testing tray to use as a control in skin testing.

I am well aware that such a crude method of extracting is open to certain theoretic objections. The main advantage is that the material examined has escaped the modifying influence of washing, drying, and chemical action which, I believe, modifies its properties to the extent that some of its antigenicity is destroyed. I admit the lack of experimental evidence to support this belief. However, comparative skin testing, using extracts prepared in various ways, convinces me that such a crude extract more often produces typical wheals by the scratch technique than do extracts prepared by more complicated and antigen-destroying methods. Also and without elaborate statistical analysis, I believe that false positive reactions are obtained in no greater frequency than with the most acceptable extracts of other types of material. Only rarely is a positive reaction obtained to the medium control.

No attempt has been made to identify properly all of the strains isolated. The majority have fallen into the aspergillus, the penicillium, and monilia-like groups. Also, we have found it difficult to maintain stock cultures without eventually obtaining growths which appear to be widely divergent from the initial growth. And we have not been able to make studies to determine any antigenic differences that might accompany morphologic or cultural variations such as we know exist among bacteria.

CLINICAL RESULTS

The patients under consideration are the ones in whom no evidence of infection can be found. We conclude that in these patients the organism probably is nonpathogenic, is present in the respiratory tract, and is not invading the tissues or producing any reaction in the host other than possibly an allergic one such as would occur if pollens of other allergens were inhaled.

The patients, in whom there is no evidence of fungus disease but from whom positive cultures are obtained, fall into two groups. In one group, repeated cultures over a period of several months will show alternating positive and negative findings. This is true even with the most careful selection of specimens and using multiple plates for each specimen. This, I think, probably represents repeated exposure by inhalation of spores from some extraneous source, which, in the course of several days, disappear from the respiratory tract by natural means.

From the other group positive cultures are obtained on each cultivation. We interpret this as a true propagation of the fungus in the bronchial secretions or constant exposure to the spores from extraneous sources.

We are not prepared to furnish a statistical analysis of the results obtained by this approach to the study of allergens in patients with asthma. We can certify that only in over a period of twelve years we have been able to relieve a significant number of otherwise refractory patients by the use of such studies and treatment.

For attempts at hyposensitization, the crude concentrated extracts are diluted in ten steps and the concentration used for the beginning dose is the one which just gives a positive intradermal test. The results with treatment in this manner are exactly the same as with pollen therapy. The usual local reactions are obtained, constitutional reactions of mild degree are obtained with the higher doses, and the usual proportion of patients are seen who cannot tolerate large doses without an accentuation of asthmatic symptoms.

I wish to apologize for presenting my ideas and opinions on this subject without the bulwark of experimental work and statistical evaluation to support them. I can plead only that the limitations of private practice impose a definite limit to the work that can be devoted to research. I think my observations have extended over a sufficient period (twelve years) to warrant consideration and I offer this short note in the hope that others may be able to support or deny them.

The co-ordinative principle of science consists in the adjustment of each scientist's activities to the results achieved by others —REVENO.

MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

VII. Further Survey Studies

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SEVERAL years ago in a review on molds in relation to asthma and vasomotor rhinitis (Morrow and Lowe, 1943[1]), we devoted one section to surveys of air-borne molds. We mentioned the different points of view which had prompted these investigations and cited twenty-five studies including the early work of some of us (Prince, Selle, and Morrow, 1934;[3] Prince and Morrow, 1937;[4] Prince and Morrow, 1939;[5] Prince, Morrow and Lowe, 1939;[6] and Morrow, Prince and Lowe, 1942[2]), who now are engaged in a study being made, in collaboration by The Association of Allergists for Mycological Investigations and The University of Texas.

In a paper in 1942 (Morrow, Prince and Lowe[2]), we were able to point out specifically the following:

1. Molds are distributed widely throughout the central and southwestern United States.
2. Certain mold groups occur as dominant forms.
3. Total counts tend to be more uniform throughout the year in the South, reaching a peak in the fall.
4. The total counts in the North rise from a winter low to a maximum in the summer and fall.
5. The high total counts in the North equal, or exceed, the ones in the South.
6. *Alternaria* and *Hormodendrum* are encountered more frequently and occur in higher numbers than any other molds.
7. With few exceptions, the high total counts observed at all stations and the low total counts in the North during the winter represent the variation of *Alternaria* and *Hormodendrum*. A seasonal rather than a regional trend of these dominant species is indicated.
8. A seasonal trend is suggested in the occurrence of *Fusarium*.
9. Although *Aspergillus, Penicillium,* and certain other species also are encountered frequently, the numbers are low and the occurrence is uniform throughout the year, neither seasonal nor regional trends being apparent.
10. *Pullularia* is striking in the fact that, when present, it occurs as a "shower" at different stations and is a major portion of the station total. Since it is observed during both winter and summer and in the North as

From the Department of Botany and Bacteriology, The University of Texas, in collaboration with The Association of Allergists for Mycological Investigations. Read at a meeting of The Association of Allergists for Mycological Investigations, San Francisco, California, June 28, 1946.

well as in the South, it would seem that the occurrence is local and not seasonal or regional.

At sixteen member stations (Dallas, Temple, Waco, Houston, Abilene, Fort Worth, San Antonio, and Galveston, in Texas, and Shreveport, Toledo, Nashville, Evanston, St. Louis, Milwaukee, Kansas City and Minneapolis) plates were exposed during the two years in which these earlier observations were made. Membership at that time included twenty-five members. Some of them, however, did not expose plates and others were represented by another member station in the same city. Since then, the membership has been extended to include some fifty members. Not all of these have exposed plates, and some have become inactive.

After three years, the charter members discontinued plate exposures, but special plates were submitted from time to time. Newer member stations include some for which we have fairly complete data (El Paso, Little Rock, Miami, Superior, Decatur, Charleston, West Virginia, Boston, Pittsburgh, Memphis, and Buffalo). Others have a more or less incomplete record as to the number of and consistency in plate exposures.

A tabulated summary (Table I) for all of the stations, indicating when plates were exposed, by the month and year, reveals some interesting facts. Among other things, it can be seen that the sixteen charter member stations of 1939 were fairly consistent during the initial two-year period and that some of them continued the survey for longer periods, whereas Portland, Oregon, entered the survey only in April, 1946.

The table shows that thirty-one stations have had exposed plates examined at the laboratory at The University of Texas. A monthly report is based on four plates examined, two each of two different exposure dates. It can be seen that more than 600 plates were examined in 1939, 1940, and 1941, each, some 400 in 1942, and a fewer number since then, a total of almost 3,000 plates. Also, it can be seen that plates examined for each station vary in number from 228 for Galveston to 8 for Portland.

A column is added at the right of the table to show the last culture isolation for each member station. This number corresponds to the number of cultures isolated for the respective stations. For example, over a three-year period, 300 cultures were isolated and studied from the Minneapolis station. When some of them were found to be identical to isolations recorded earlier and kept as stock cultures, they were discarded, thus reducing the number of stock cultures for each station from the total number of isolates made. More than 5,000 cultures have been isolated and studied, varying from 4 for Portland to 686 for Houston, and the numbers for the respective stations are a reflection, in large part, of the period of participation in the survey by each station.

For the qualitative mold picture, certain stations were selected.

For one of the newer stations, Buffalo, plates were examined from September, 1944, through September, 1945. Table II shows the mold incidence during this period. Numbers for the total molds and the different

TABLE I. SUMMARY OF ALL STATIONS

Station	1939												1940												1941												1942											
	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D
Abilene	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	−	−	+	−	−	+	−	−	−	+	−
Dallas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−
Ft. Worth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−																								
Galveston	+	+	+	+	+	+	−	−	−	+	+	−	−	−	+	+	−	−	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Houston	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
San Antonio	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−
Temple	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	−	+	−	−	+	−																									
Waco	−	−	+	−	+	+	+	+	+	−	+		+	−	−	−	−	+	−	−	−	−	+																									
Shreveport	+	+	+	+	+	+	+	+	+	+	+		+	−	+	+	−	−	−	−	−	−	−																									
St. Louis	−	−	+	+	+	+	+	+	+	+	+		−	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	−	−	−											
Kansas City	+	+	+	−	+	+	+	+	+	+	+		+	+	−	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
Nashville	+	+	−	+	+	+	+	+	−	+	−		+	−	+	−	−	+	+	+	+	−	−		+	+	+	+	+	+	+	+	+	−	−	−											
Evanston	+	−	+	+	+	+	+	−	+	−	−		−	+	+	+	+	−	+	−	−	−	−		−	−	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Milwaukee	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	−	−																									
Minneapolis	+	+	+	+	+	+	+	−	+	+	+		+	+	+	+	+	+	+	+	+	−	−		+	+	+	+	−	−	−	−	−	−	−	−	+	+	+	+	−	−	−	−	−	−	−	−
Toledo	+	−	−	−	+	+	+	+	+	+	+		−	−	+	+	+	+	+	+	+	−	+		+	+	−	+	+	+	+	+	+	−	−	−											
El Paso													−	−	−	−	−	+	+	+	+	−	−		+	+	−	+	+	+	+	+	+	−	−	−											
Little Rock													−	−	−	+	+	+	+	+	−	+	−		−	+	−	−	−	−	−	−	−	−	−	−											
Austin																									−	−	−	−	−	−	−	+	−	−	−	−	−	+	−	+	+	+	−	−	−	−	−	−
Miami																									−	−	−	−	−	−	−	+	+	+	−	−	−	+	+	−	−	−	−	−	−	−	−	−
Superior																									−	−	−	−	−	−	−	−	+	+	+	+	+	+	+	+	−	−	+	+	+	+	−	−
Decatur																									−	−	−	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Charleston																									−	−	−	−	−	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Boston																									−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cleveland																																					−	−	+	+	+	+	+	+	−	−	+	−
Pittsburgh																																																
Ann Arbor																																																
Memphis																																															
Detroit																																															
Buffalo																																															
Portland																																															
Plates examined	672												668												608												424											

Station	1943 J	F	M	A	M	J	J	A	S	O	N	D	1944 J	F	M	A	M	J	J	A	S	O	N	D	1945 J	F	M	A	M	J	J	A	S	O	N	D	1946 J	F	M	A	M	J	J	A	S	O	N	D	Isolates
Abilene	+	−	−	+	−	+	+	−	−	−	−	−	+	−	−	−	−	−																															208
Dallas																																																		320
Ft. Worth																																																	89
Galveston	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	−	+	−	−	−	−																			367
Houston																									−	−	−	−	+	+																			686
San Antonio																																																	373
Temple																																																	166
Waco																																																	53
Shreveport																																																	109
St. Louis																																																	291
Kansas City																																																	320
Nashville																																																		84
Evanston	−	−	−	−	−	+	−	−	−	−	−	−	+	+	+	+	+	−	+	−	−	−	−	−																									180
Milwaukee																																																	105
Minneapolis																																																	300
Toledo																																																		242
El Paso																																																	136
Little Rock																																																	29
Austin																																																	29
Miami																																																	20
Superior																																																	60
Decatur	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−																									335
Charleston																																																	112
Boston	+	+	+	−	−	−	−	−	−	−	−	−																																					154
Cleveland																																																	27
Pittsburgh	−	−	−	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	−	+	−	−	+	+							185
Ann Arbor	−	−	−	−	−	−	−	−	−	−	+	+													−	−	−	+	−	+																			24
Memphis	−	−	−	−	−	−	−	−	−	−	−	+	+	+	+	+	+	+	−	+	+	+	+		+	−	−	−	−	−	−	−	−	−	+		+	−	−	−								67
Detroit													−	−	−	−	−	−	−	−	+	−	−																											13
Buffalo													−	−	−	−	−	−	−	−	+	+	+	+	+	+	+	−	+	+	+	+	−	−	−		−	−	−	−	+									84
Portland																																					−	−	−	+	+										4
Plates examined	152												188												104												28												Total	5172
																																			2844													

Member stations submitting exposed plates by years and months. Totals for the year based on four plates examined each month marked (+).
Cultures isolated and studied for each station appear in the column at the extreme right. Isolates for each station are recorded and stocked by number (W-1 through W-300 for Minneapolis).

TABLE II. BUFFALO, NEW YORK

FUNGI	Month	1944												1945												1946					
		J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J
	Plates	−	−	−	−	−	−	−	−	+	+	+	+	+	+	+	−	+	+	+	+	+	−	−	−	−	−	−	−	+	
Total										16	13	1	10	3	0	9		4	4	5	6	4								3	
Hormodendrum										2	2		2			3		1		2											
Botrytis										2																					
Alternaria										5	4		1	1				1			1	1								1	
Pullularia										2			1			1					1	2								1	
Torula										2	1	1	1	1						1											
Sterile sp. dark										2			1			1														1	
Nigrospora										1																					
Sterile sp. pale											4		1			2		2			1	3									
Penicillium											2		2			1			3			1	1								
Aspergillus													1			1				2											
Paecilomyces														1																	

Total	78	Penicillium	10	Aspergillus	4
Alternaria	15	Torula	8	Botrytis	2
Sterile sp. pale	13	Pullularia	7	Nigrospora	1
Hormodendrum	12	Sterile sp. dark	5	Paecilomyces	1

TABLE III. MEMPHIS, TENNESSEE

FUNGI	Month	1943						1944										1945												1946					
		J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J
	Plates						+	+	+	+	+	+	−	+	−	+	+	+	+	+											+						
Total							1	0	7	1	2	10		8		9	8	6	6	8										0	0						66
Verticillium							1																														1
Hormodendrum									1		1	2		2		1	2	1	1	2																	13
Pullularia									1							1			1	1																	4
Torula									1																												1
Alternaria									1			2		1		1		1		2																	8
Sterile sp. pale									1			4				1	1	1	1	2																	11
Pennicillium									1			1		2		1	1																				6
Paecilomyces									1																												1
Pycnidial sp.										1																											1
Actinomycete											1																										1
Rhizopus												1																									1
Trichoderma														1																							1
Fusarium														1		1																					2
Sterile sp. dark														1		1	1																				3
Spondylocladium																1																					1
Oospora																1			2																		3
Aspergillus																	2	2	1	1																	6
Mucor																		1																			1

Total	66	Pullularia	4	Peacilomyces	1
Hormodendrum	13	Sterile sp. dark	3	Pycnidial sp.	1
Sterile sp. pale	11	Oospora	3	Actinomycete	1
Alternaria	8	Fusarium	2	Rhizopus	1
Penicillium	6	Verticillium	1	Trichoderma	1
Aspergillus	6	Torula	1	Spondylocladium	1
				Mucor	1

TABLE IV. PITTSBURGH, PENNSYLVANIA

FUNGI	Month	1943												1944												1945												1946					
		J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	
	Plates	−	−	−	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	
Total						15	10	5	10	12		3	2	2	4	6	1	8	2	14	5	13	4	7		1	2	13	6	5	4	9	4	11	4			5			0	0		187
Penicillium						5	1		1	1			1		1	1	1			2		2	1	1				3							1									22
Oospora						1																						1															2
Sterile sp. pale						5	2	2	2	1		2		1				1	1		3	1	1	2			1		2	1	3		2										33
Hormodendrum						1	3	1	1	2								1	2			2		1			1	2	2		3	1	2					1					26
Pullularia						1				2		1	1		1	1		2		3		3		1	1		2	1				1	2	1									24
Trichoderma						1				1						1							1			1			2													7
Undetermined sp.						1	1	1										1														1											5
Alternaria							3	1	2	4				1		1				1	1	2		1				1		1	3	2	2	2			1						29
Sterile sp. dark									1									2		3			1						1				1									9
Bulbiferous sp.									1																																		1
Aspergillus									2	1						1					1					1	4												1					11
Torula														2				1				2				2	1												2					11
Yeast																1				2																							3
Fycnidial sp.																		1																									1
Monilia																				1																							1
Verticillium																						1																					1
Spondylocladium (Curvularia)																								1																			1

Total	187	Aspergillus	11	Oospora	2
Sterile sp. pale	33	Torula	11	Bulbiferous sp.	1
Alternaria	29	Sterile sp. dark	9	Fycnidial sp.	1
Hormodendrum	26	Trichoderma	7	Monilia	1
Pullularia	24	Undetermined sp.	5	Verticillium	1
Penicillium	22	Yeast	3	Spondylocladium	1

genera are recorded; no species are indicated in the tables. Of *Hormodendrum* and *Alternaria,* counts of two and five were observed in September when the total count was sixteen. In the summary column on the right, grand totals are indicated for the thirteen-month period, *Hormodendrum* and *Alternaria* being twelve and fifteen of the total count of seventy-eight. The order in which the eleven genera appear in the table is that in which the molds appeared on the plates, beginning with the first plate examined. Below the table, the genera are listed in the order of their relative appearance, based on the total number of different molds isolated during the observation period. The ones most frequently encountered were *Alternaria,* unidentified sterile pale species, *Hormodendrum, Penicillium, Torula, Pullularia,* unidentified sterile species, and *Aspergillus,* in the order named.

Seasonal aspects can be noted. They are discussed in detail in longer reports which are sent to members from time to time. It can be seen that seven of the eleven genera appeared in September, two others were added in October, and one each in December and January. Only *Botrytis, Nigrospora,* and *Paecilomyces* were limited to a single appearance each.

Memphis, participating a year, February, 1944, to February, 1945, is tabulated similar to Buffalo (Table III) and a comparison is interesting. The dominant molds include *Hormodendrum, Alternaria,* unidentified sterile pale species, *Penicillium, Aspergillus* and *Pullularia,* the last two being confined to the fall-winter period. No great difference between Buffalo and Memphis was noted in the number of totals and the different genera. There was a larger number of molds which occurred only occasionally throughout the year, including those confined to a single month, such as *Torula, Paecilomyces,* unidentified pycnidial species, *Trichoderma, Verticillium, Rhizopus, Mucor, Spondylocladium,* and an actinomycete. *Alternaria* counts were high in May and January, *Hormodendrum* in May, July, October, and January, and *Aspergillus* in the fall and winter only. Memphis might be expected to have a local problem in mold allergy during a given month when these occasional forms appear on the exposure plate.

Pittsburgh was studied for almost three years. Tabulated, the picture is striking (Table IV). Actually, no more species were encountered in three years for Pittsburgh than for Memphis in one year. Moreover, with the exception of several species occurring but once each in 1944, the qualitative picture is similar for 1943, 1944, and 1945.

What then are the mold possibilities, as one reads the table, when considering a patient with allergy caused by molds? The dominant molds include unidentified sterile pale species, *Alternaria, Hormodendrum, Pullularia, Penicillium, Aspergillus, Torula,* unidentified sterile dark species, and *Trichodermæ;* yeasts and *Oospora* are possibilities, and the ones occurring in only one month each, unidentified bulbiferous and pycnidial species, *Monilia, Verticillium,* and *Spondylocladium.*

TABLE V. DECATUR, ILLINOIS

FUNGI	Month	1941						1942												1943												1944												
		J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	
	Plates	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	
Total		16	4	5	8	1	11	1	5	13	11	7	6	3	9	17	9	5	3	2	24	7	19	5	14	5	10	5	2	14	0	5	9	17	11	6	17	15					357
Alternaria		9	2	2	2	1	2		1	3	2	4	3	3	2	5			1	1	3	3	4	3	7	4	2	3	1			2	1	3	4	3	7	5					98
Aspergillus		1							1	1	2	1				1	1	1			1		1							1							1							13
Penicillium		1		1	1			1	1	1	2						4	1	1	1			3		5	2	1			2		1				1							31
Mycogone		3	1		2		3			2	1	1	2				1						1		3																			20
Actinomycete		1																																										1
Hormodendrum		1	1	2	2		3		1	3	1	1			4	3			1		6	1			1	2	1	4	1	1	1		1	2	4	2	1	1	3					55
Pullularia					1		3		1	3	3					3					2		2					1				1	1	2										24
Undetermined sp.													1			2					2	2	1	3										1	1		1							14
Sterile sp. pale															3	2	3	2			5	1	3		2		1	1	1				2	1			1	3						31
Fusarium																1					2		1		3									4		1		2						15
"Bodies" sp.																	1																											1
Mucorales sp.																					1																							1
Curvularia																					1														1				1					3
Absidia																						1																						1
Phoma																						1	2		2	1			1					1		2								10
Sterile sp. dark																								1	1									1		1			2	1				7
Metarrhizium																									1																			1
Yeast sp. black																										1																		1
Trichoderma																											1																	1
Pycnidial sp.																												1							1									3
Syncephalastrum																													1															1
Sclerotial sp.																																1			1									2
Monilia																																				1									1
Nigrospora																																				1									1

Total	357	Fusarium	15	Curvularia	3	Yeast sp. black	1
Alternaria	98	Undetermined sp.	14	Actinomycete	1	Trichoderma	1
Hormodendrum	55	Aspergillus	13	"Bodies" sp.	1	Syncephalastrum	1
Penicillium	31	Phoma	10	Mucorales sp.	1	Monilia	1
Sterile sp. pale	31	Sterile sp. dark	7	Absidia	1	Nigrospora	1
Pullularia	24	Sclerotial sp.	2	Metarrhizium	1		
Mycogone	20	Pycnidial sp.	3				

TABLE VI. GALVESTON, TEXAS

FUNGI	Month	1939												1940												1941												
		J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	
	Plates	+	+	+	+	+	+	−	−	−	+	+	−	−	−	+	+	+	−	−	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Total		8	11	10	12	7	7				13	7			6	19	24							1	9	5	6	16	15	7	3	4	5	6	0	0	10	211
Alternaria		4		5	5	4					2					9	14							1	2		2		4	1		1					3	57
Helminthosporium		2				1	1				1	1																	2			1	1					10
Penicillium		1	2				1																			2	2	1	1	1	1	1	1				1	15
Sterile sp. pale		1	1		1		1				2	1				3										1	1	1	1	1	1			1			2	19
Hormodendrum			1	4	5	2					5	2			5	7	5							2		1	1	2	2	1	1			1			2	49
Aspergillus			1		1						1															1												4
"Bodies" sp.			1				1																														2
Spondylocladium							1				1	3																				2						7
Fusarium			2				1				1				1		5							1			1	3	2	1								18
Mycogone																																	1			1		2
Phoma																								1			1	1										3
Pullularia																										1	1	1	2	1			1			1		8
Stemphylium		1	1																											1								3
Curvularia																																1	1					2

Total	211	Penicillium	15	Phoma	3
Alternaria	57	Helminthosporium	10	Stemphylium	3
Hormodendrum	49	Pullularia	8	Mycogone	2
Sterile sp. pale	19	Spondylocladium	7	Curvularia	2
Fusarium	18	Aspergillus	4	"Bodies" sp.	2

TABLE VII. GALVESTON, TEXAS

FUNGI	Month	1942												1943												1944												1945					
		J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J
	Plates	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	−	+	−	−	−	−
Total		5	7	6	3	6	8	2	2	2	16	1	14	7	2	8		2	17	5	3		12	8	5	8	21	21	14	7	18	1		7	12		2		12					263
Alternaria			2	1	1	2	2	1			2		2	3		1		1					1	1		2	5	1	2	1	1	1		1	1		1							36
Helminthosporium				1		1	1						1			1							1	1		1	1	1	1					1										12
Penicillium		1			1	1	1			1	2		1			1		1		1			2		1	1	3	2	1		2			2	1				1					27
Sterile sp. pale									1		2	1				1			17	2			1			1	1	2	1		1		1		1			4					37
Hormodendrum		1	4	2		1	2				1		3	3		2							2	1	1	1	2	3	3		3			1	4				1					38
Aspergillus		1			1		1				3		3	1							1		1	1			1	2	1	1	1								1					20
"Bodies" sp.																																												0
Spondylocladium						1																	1	2										1	1									6
Fusarium											3		3			1													1															8
Mycogone									1						1													2		1													5
Phoma			1																																								1
Pullularia		1		2				1								1				1								1					1										8
Syncephalastrum										1											1		1	2	1	1	1	1		2	3							2					14
Undetermined sp.											2		1		1												2	1	1														8
Pycnidial sp.																				1								2	1		1												5
Paecilomyces																					1																						1
Yeast sp.																							2	1																			3
Sterile sp. dark																								1				2	2	1	1				1			1					8
Sclerotial sp.																											1	5							1									7
Torula																1											1	1											1					4
Oospora																											1	1															2
Trichoderma																											1		1	1				1				1					5
Nigrospora																											1																1
Cephalosporium																														1													1
Stachybotrys																														1													1
Mucorales sp.							1																																				1
Sporotrichum											1																																	1
Verticillium																																		1										1

Total	263	Helminthosporium	12	Mycogone	5	Paecilomyce	1
Hormodendrum	38	Fusarium	8	Pycnidial sp.	5	Nigrospora	1
Sterile sp. pale	37	Pullularia	8	Trichoderma	5	Cephalosporium	1
Alternaria	36	Undetermined sp.	8	Torula	4	Stachybotrytis	1
Penicillium	27	Sterile sp. dark	8	Yeast sp.	3	Sporotrichum	1
Aspergillus	20	Sclerotial sp.	7	Oospora	2	Verticillium	1
Syncephalastrum	14	Spondylocladium	6	Phoma	1		

The appearance of *Trichoderma* is always interesting for it may be an indicator of textile deterioration—moldy clothing, tenting, rope, uniforms of the armed forces, and even the seabag. *Chaetomium* is another of the textile-rotting fungi, but it is noted less frequently on an air-exposure plate.

Whereas the picture for Pittsburgh was more or less consistent over three years, that for Decatur shows a number of molds appearing for the first time from year to year. One might think that industrial Pittsburgh would have a more changing aerobiology than the more rural Decatur. The table for Decatur (Table V) is interesting to study. Decatur has a more nearly perfect exposure record than any of the member stations; not one month did plates fail to come to the laboratory. The dominant molds include the usual *Alternaria, Aspergillus, Penicillium, Hormodendrum,* an unidentified sterile pale species, and *Pullularia;* the somewhat less usual *Fusarium* and *Phoma,* with several appearances each of *Mycogone,* unidentified sterile dark, sclerotial, and pycnidial species, and *Curvularia.* Ten species were noted only once each, and fourteen undetermined species made the list higher for Decatur than for any of the stations studied since the sixteen charter stations were retired. *Phoma* might be a problem there; also, a local problem might accompany the succession of species making a single appearance each from time to time.

The Galveston station exposed plates for more than five years (Tables VI and VII). The picture is "spotted" for 1939 and 1940, but fairly complete for 1941, 1942, 1943, and 1944. The dominant molds include ten genera, with the appearance of fourteen to ninety-three over the five-year period, such as *Alternaria, Hormodendrum,* unidentified sterile pale species, *Penicillium, Aspergillus, and Pullularia.* By adding the totals and corresponding genera in the two tables, it can be seen that the order changes little in the early and later periods. Only six of thirty genera made a single monthly appearance, *Paecilomyces, Nigrospora, Cephalosporium, Stachybotrytis, Sporotricum, and Verticillium.* There is an interesting point in connection with the place of dominance of *Alternaria,* with 93 appearances in the 574 total molds for Galveston. Some of us (Prince, Selle and Morrow) did not even list *Alternaria* with the molds reported in 1937 from Galveston.[4] From the later results, it can be seen that *Alternaria* is the one mold that was recovered each month of each year during the period of more than five years.

Again speculation is invited as to a possible problem at Galveston with the occasional molds which indicate seasonal groups in many instances, such as *Nigrospora, Trichoderma, Oospora,* and *Paecilomyces,* which appear only in the spring months.

Three points seem outstanding in these results which have been presented.

First, there is a "top ten" group of genera for all stations, which include the dominant ones in nearly every instance when they are shown for a station, whether studied for one year, two, or five:

Alternaria	*Aspergillus*	*Torula*
Hormodendrum	*Pullularia*	*Fusarium*
Penicillium	Sterile pale species	*Trichoderma*
	Sterile dark species	

Secondly, in the ten dominant molds for all stations there is a "big six" for each station, which may or may not be seasonal. For the stations discussed in this report they can be listed as follows:

Buffalo	Decatur	Memphis
Alternaria	*Alternaria*	*Hormodendrum*
Sterile pale species	*Aspergillus*	*Alternaria*
Hormodendrum	*Penicillium*	Sterile pale species
Penicillium	*Hormodendrum*	*Penicillium*
Torula	Sterile pale species	*Aspergillus*
Pullularia	*Pullularia*	*Pullularia*

Galveston	Pittsburgh
Alternaria	Pale sterile species
Hormodendrum	*Alternaria*
Sterile pale species	*Hormodendrum*
Penicillium	*Pullularia*
Aspergillus	*Penicillium*
Pullularia	*Aspergillus*

The third point concerns the occasional types. May they not be significant not only as a part of the total aerobiology picture for a particular station, but possibly as the factor in many stubborn clinical cases of inhalant respiratory allergy of which the cause does not fall into the better known mold groups? An analysis of surveys is heartening to the physician who does routine testing with the "top ten" or the "big six," but may he not be challenged also by *Trichoderma* that appears only in May or *Rhizopus* in October in his particular area? We cannot discount them, and we should remember that a single colony on a two-minute plate theoretically is equivalent to a pollen count of twenty-one (Prince and Morrow, 1937).[4]

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MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

VIII. Mold Allergy in West Texas—Clinical Observations

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A STUDY of incidence of molds in the Abilene, Texas, area has been conducted by us since 1938. A part of this study is included in the general survey made by the Association of Allergists for Mycological Investigation, under the supervision of Dr. Marie B. Morrow and her associates, of the University of Texas. Dr. Homer Prince, of Houston, Texas, especially deserves credit for initiating this work.

Dr. Morrow's tabulations, compiled from plate agar exposures obtained from various stations over the country, are recorded elsewhere. Her survey has been of great value to all of us interested in this field. From the beginning, however, we have felt that exposed slide counts also give valuable information. Such slide counts have been made daily in Abilene since 1938 and tabulated with daily pollen counts which were begun years earlier. The difference in the form and structure of the spores on the exposed slides makes accurate differentiation impossible, but the daily study of the slides gives a fairly reliable index of the general incidence of the molds.

Alternaria forms are identified readily and a tabulation of this group gives a helpful picture of the molds in general in this section where *Alternaria* is the most numerous of the dominant groups. *Alternaria* occurs throughout the year in Abilene. The counts are lower in the earlier months of the year and increase in May, with intermittent high counts well into December. According to Dr. Morrow's report, this seasonal incidence is more marked in the North and Middle West than in the South and Southwest.

This seasonal incidence of *Alternaria* and other molds is of definite clinical importance. In our section, pollinosis is perennial. The important offenders are mountain cedar, the ragweeds, the Chenopodiales group, the grasses, and certain trees, particularly mesquite and oak. The *Alternaria* counts consistently are higher than any of the pollen counts, except during brief periods in the fall and winter when the mountain cedar peaks are extremely high. The molds may cause inhalant allergic symptoms at any season and add to confusion in diagnosis during periods when both molds and pollens are high.

In this study we have reviewed the records of 392 new patients with inhalant allergy, encountered in private practice in a five-year period from 1941 through 1945. Inhalants used in testing included common pollens, familiar miscellaneous inhalants, and eight mold extracts. The mold ex-

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TABLE I. SYMPTOMATOLOGY
(392 Cases Inhalant Allergy)

	Asthma No.	%	Hay Fever No.	%	As. & H.F. No.	%	Misc. Conditions No.	%
Molds only	13	3.3	10	2.2	6	1.5	4	1.0
Mixed molds	45	11.4	59	15.0	25	6.3	12	3.0
Total	58	14.7	69	17.6	31	7.8	16	4.0

TABLE II. AGE INCIDENCE
(174 Cases Reacting to Molds)

	Total	1-20 Years No.	%	Over 20 Years No.	%
Cases Reacting to Molds Only	33	25	75.7	8	24.2
Cases Reacting to Molds and Other Inhalants	141	71	50.3	70	49.6

tracts were prepared by Dr. Prince from cultures which were isolated by Dr. Morrow from exposed plates submitted by various members of this Association. Extracts used were those of *Alternaria, Aspergillus, Curvularia, Fusarium, Helminthosporium, Hormodendrum, Spondylocladium,* and *Penicillium.* All testing was done by the intracutaneous technique. Only moderately or strongly positive reactions were tabulated in this study.

Of the 392 patients, 174, or 44.3 per cent, gave reactions to one or more mold extracts. Thirty-three of the patients, or 8.4 per cent, reacted only to molds. One hundred forty-one, or 35.9 per cent, gave reactions to molds and other inhalant extracts.

Of the 392 patients with inhalant allergy, fifty-eight, or 14.7 per cent, with asthma reacted to molds. Thirteen, or 3.3 per cent, of them reacted only to molds. Sixty-nine, or 17.6 per cent, with hay fever reacted to molds, with 10, or 2.2 per cent, reacting only to molds. An additional group of thirty-one patients, having both asthma and hay fever, added to these figures. Sixteen patients had symptoms of inhalant allergy other than asthma and hay fever, chiefly allergic rhinitis or allergic bronchitis (Table I).

The age of patients who manifest mold sensitivity is of particular interest to us. Of the 392 cases, ninety-six sensitive to molds were in the early age group, one to twenty years. Seventy-eight sensitive to molds were over twenty years of age. Of added interest was the fact that of thirty-three patients reacting only to molds twenty-five, or 75.7 per cent, were in the youngest age group (Table II). From general observation, especially in the last two years, we have been impressed even more with the importance of mold sensitivity in children. From January to June, 1946, the incidence showed a relatively high percentage of mold sensitivity in the younger age group.

Passive transfer studies were not made routinely in the clinical testing

of these patients. The method was used repeatedly, however, in experimental studies. We have never failed, on trial, to effect a passive transfer with a serum of a patient sensitive to mold extracts. We have used the method of exhaustion of passively transferred sites, in an attempt to determine whether or not a common atopen is present in extracts of the various mold species. Limitation of time and space prevents a detailed report of these experiments. We gained the impression, but an impression only, that there were common atopens in extracts of certain groups. On the contrary, extracts of the dominant *Alternaria* group consistently did not desensitize sites sensitized to *Curvularia, Spondylocladium,* or *Hormodendrum.*

TREATMENT

This is only a brief summary of results from treatment. We have tried to tabulate these results from an objective standpoint and only from a perusal of the records. Of the thirty-three patients sensitive only to molds, twenty-one, or 63.6 per cent, gained complete or marked relief from symptoms. Of the 141 patients sensitive to molds and other inhalants, seventy, or 49.4 per cent, obtained satisfactory results from treatment.

We feel that these results, although not striking, are distinctly worth while. Results of treatment in the pure mold-sensitive group compare favorably with results in the pure pollen-sensitive group.

SUMMARY

1. A study of exposed slides over a period of five years has shown that molds are present throughout the year in the Abilene, Texas, area. A study of exposed agar plates have corroborated this observation. Proper identification of the various molds can be made only after isolation from agar plates. Both methods are of value. *Alternaria* forms are readily identified by the slide counts, and they and other identified forms should be included in pollen counts.

2. Of 392 new patients with inhalant allergy, studied over a five year period, 1941 to 1945, 174, or 44.3 per cent, gave definite reactions to one, or more, of the mold extracts. Thirty-three cases, or 8.4 per cent, gave reactions only to molds.

3. In the younger age group, one to twenty, mold sensitivity particularly is prevalent.

4. Therapy by desensitization is worth while.

The authors wish to thank Miss Nell Glass and Miss Inez Darden for technical assistance in these studies.

THE INCIDENCE OF IDIOBLAPTIC CIGARETTE SENSITIVITY

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THE choice of the title of this communication may strike some as odd and indeed too wanting in exactness from the point of view of the specificity of allergic sensitivity to be scientifically acceptable. Nevertheless, this study of the frequency of idioblaptic sensitivity to cigarettes among subjects of that category of allergic disease may be justified because of the greatly preponderant preference of smokers for tobacco in that form. Moreover, for a number of reasons, it would be impracticable to attempt such a study as this with the separate components of the commercial cigarettes.

The published reports with which the present one can best be compared or contrasted are the well-known ones of Harkavy and of Sulzberger. Both of these investigators examined subjects with respect to the possible presence of cutaneous sensitivity to tobacco, employing extracts of pure tobacco in the familiar intracutaneous tests, and both reported an unusually high percentage of positive reactions following direct tests in subjects with thromboangiitis obliterans.

In three series of such patients, Harkavy and his associates found 83, 86 and 87 per cent of positive reactors. Sulzberger and Feit in a smaller series of twenty-four cases of (thromboangiitis obliterans) found 78 per cent positive.

It is noteworthy that Harkavy[4] found in a control series of smokers 20 per cent and in non-smokers 12 per cent of positive reactors. Of obvious significance is the report of Sulzberger and Feit[5] that passive transfer of the cutaneous sensitivity (Prausnitz) failed in twenty-one of the twenty-two patients with thromboangiitis obliterans, nineteen of whom showed positive intracutaneous reactions in the direct tests. The one patient whose serum contained passively transferable anti-tobacco reagin was, in like manner, found to be reaginically more sensitive to house-dust than to tobacco. This result is reasonably comparable with that reported by Aaron Brown[1] among his asthmatic patients—about 1 per cent were reaginically sensitive to tobacco.

Sulzberger and Feit[5] write:

"Our findings of the general lack of reagins, in spite of immediate wheal reactions to tobacco in thromboangiitis obliterans, is in contradiction to the results of Harkavy et al†. These observers report that the wheal hypersensitivity to tobacco is associated with the presence of 'atopic reagins' to tobacco in thromboangiitis obliterans; and that they were able to demonstrate such reagins in thirteen out of twenty tobacco-positive cases of thromboangiitis obliterans. And that: 'The presence of reagins to tobacco in these thromboangiitis cases indicates that we are dealing

†Harkavy, Hebald and Silbert: Proc. Soc. Exper. Biol. & Med., 30:104-107, 1932

with individuals who were in all probability atopic, and that the positive phenomena are true antigen-antibody reactions.'"

Sulzberger and Feit[5] remark further:

"However, our above reported results must classify thromboangiitis obliterans as a condition usually associated with a specific and marked hypersensitivity of the vascular apparatus of the skin to tobacco, but without any at present demonstrable connection with asthma, hay fever, and disseminated neurodermite, et cetera, and, in our cases, without regularly demonstrable reagins." (authors' italics)

Some years ago, I had some part in arranging for an investigation of this question in a hospital service specializing in the study and management of thromboangiitis obliterans. The tests were carried out by an experienced investigator, Katherine L. Bowman, with ample clinical material and controls and with the skillful use of the Prausnitz experiment. The results confirmed those of Sulzberger and Feit in the clearly demonstrated absence of reaginic sensitivity to tobacco to any noticeable extent more in the thromboangiitis obliterans group than in the control group.

Miss Bowman summarized her hitherto unpublished findings as follows:

"1. Comparing the results obtained by testing sixty-nine thromboangiitis obliterans patients and sixty normal smokers with tobacco and other allergens, it was found that there is practically no difference in the percentage of positive reactions to tobacco in the two groups, if one-plus and plus-minus reactions be disregarded.

"2. If the one-plus and plus-minus reactions be included, the difference between the percentage of postive reactions to tobacco obtained in the thromboangiitis obliterans group and that obtained in the normal group is not of sufficient magnitude to be significant.

"3. The skin response to histamine 1:1000 was found to be slightly greater in the thromboangiitis group than in the normal group.

"4. The incidence of positive reactions to ragweed pollen, timothy pollen, and horse dander, was found to be equal in both groups, showing the same distribution of allergy in the two series.

"5. With one exception, passive transfer of the tobacco reactions in the thromboangiitis obliterans group was successful only when a positive passive transfer was obtained with one or more of the other allergens tested.

"6. The incidence of positive tobacco reactions was found to be even higher in a group of twenty-three normal nurses than in the group of sixty normal men.

Conclusions

"1. There is no evidence in this study to indicate that there is a higher incidence of *specific* cutaneous sensitivity to tobacco in thromboangiitis patients than in normal men.

"2. Any slight excess in the number of one-plus reactions to tobacco which may have been found among the thromboangiitis obliterans cases might possibly be due to the same factor which is responsible for the increase in the response by this group to the nonspecific excitant, histamine 1:1000."

It is seen that Miss Bowman agrees with Sulzberger and Feit in denying the existence of a reaginic (transferable) sensitivity to tobacco as characteristic of thromboangiitis obliterans. However, her findings do not

support the conclusion of those investigators that thromboangiitis obliterans is "usually associated with a specific and marked hypersensitivity of the vascular apparatus of the skin to tobacco without regularly demonstrable reagins."

In the extended study in the past ten years of over one hundred patients affected with idioblaptic allergy, I have encountered a number of instances of nonreaginic sensitivity to cigarette-smoke as recognized by symptoms and accompanying specific tachycardia. In the greater part of this period, I tested only the habitual smokers in this respect, overlooking the possibility that exposure to the smoke of others can suffice to cause allergic symptoms, and forgetting that the constitutional nonreaginic sensitivity to an allergen is frequently established long before the subject has arrived at the age of *symptomatic* reactivity.

Soon after the first instances of symptomatic cigarette sensitivity were identified, all new patients were requested not to smoke while the early exploratory tests were being carried out; and I was astonished to find that in a few instances cigarette smoke was the sole pulse-accelerating allergen and that all symptoms disappeared shortly after smoking was discontinued.

Case 1.—In J. B., a chemist, the allergic symptoms, that is, those which disappeared in the period in which the subject reduced his smoking to a mere evening test (one cigarette), were *abnormal tiredness,* "nervous indigestion," severe headaches, neuralgia, et cetera. The daily pulse range in the period (barring the test) was 68 to 78. The highest count while smoking was 92.

Case 2.—In Mrs. S., aged twenty-eight, the allergic symptoms (meaning in this case also those that disappeared permanently after she discontinued smoking) were "deadly tiredness," nervousness, fearfulness, constant "chest colds," painful, crampy menstruation and constipation. After avoidance of smoking, the pulse range of this patient was 70 to 76. The highest count while smoking was 100.

Three patients have been observed in whom petit mal (two) or grand mal (one) seizures have been induced by cigarette smoke or smoking.

In the first of these, a petit mal reaction followed within a few minutes after the patient (M. S., eleven years old) began breathing through the folds of a handkerchief into which cigarette smoke had just been breathed.

In the second epileptic patient (M. A., eighteen years old) a lumbar sympathectomy (Danzis) had left only a small list of dietary allergens, chiefly egg. Over a period of three months thereafter, she was in daily technical service without seizures. On two occasions in that period while she was avoiding all food allergens, she was heavily exposed at her apartment to cigarette and cigar smoke. Each time she suffered a seizure, once without convulsion and once with typical grand mal convulsions. On both occasions the seizure occurred very soon, within about a half hour, after the exposure to the smoke.

The third epileptic patient (J. K., aged thirty) who had been avoiding his ten pulse-accelerating food categories and tobacco for eight months and had been free from seizures during that time, deliberately induced a grand mal seizure by smoking cigarettes. The smoking began on a Friday evening. On waking Saturday morning, the subject experienced sensations that he recognized as those customarily

presaging a seizure. He resumed smoking and in the late morning fell in a major convulsive seizure in which he was attended by a nearby physician, who recognized the condition as epileptic and prescribed dilantin. The patient disregarded the prescription. He has not smoked in the succeeding five years and has observed his rather stringent dietary restrictions. In that period there have been no seizures.

In the past few years, I have had more frequent occasion to test allergic persons for nonreaginic sensitivity to cigarette smoke, and had acquired an impression that this particular sensitivity is perhaps more common than any other. My special examination of this question has amply confirmed that impression, although the number of suitable persons at disposal for the study is not sufficient to permit anything more than an approximate estimate of the percentage incidence of cigarette sensitivity among the population.

The reference to "suitable persons" calls for explanation. The satisfactory identification of an allergen through the criterion of specific tachycardia can usually be made only if the individual's normal pulse range is known and if he is not, at the time of the test, under some food-allergic influence. For example, L. B., whose pulse rose from 60 to 69 while smoking was not on that account allergic to cigarettes because her normal range is known to be 58 to 70; but the rise in Dr. J. from 60 to 72 indicated sensitivity in this patient since his normal range is 58 to 62. On the other hand, if the test is made several hours after a meal when the pulse is steady, a rapid rise of 16 beats or more, especially if the highest count is 88 or higher, clearly indicates specific sensitivity to cigarette smoke, even if the subject's pulse character has not been determined.

Before taking up the statistical survey of cigarette sensitivity, it is necessary to discuss a certain interpretative complication.

Tobacco occupies a special position among allergens by reason of the high primary toxicity of its characteristic chief alkaloid nicotine. Hence, the question arises how shall one distinguish the toxic symptoms of tobacco from the allergic; and since this question applies, in the present discussion, only to man it would seem to be a reasonable requirement that the study of the primary toxic effect of tobacco be made in persons known to be free from familial allergy. However, since only about 10 per cent of the population can qualify in that respect, it may be considered probable that most of the human subjects who have served as experimental material in such studies were allergic, and it is conceivable that they *may* have been *selected* because of their susceptibility to tobacco, which was not recognized as allergic.

The symptoms of "tobacco-poisoning" such as commonly occur in smoking, are just those that are sometimes observed in persons who are extremely allergic to nontoxic foods—"burning in the mouth, a scratching sensation of the pharynx, increased salivation (later dryness in the mouth), headache, vertigo, confusion, disturbed vision and hearing, nausea,

TABLE I. PULSE RECORDS OF SMOKING TESTS IN CIGARETTE-SENSITIVE PERSONS

Subject	Sex	Normal Pulse Range	Rate Before Smoking	Rate at Intervals After Starting Smoking Time in Minutes							
				3′	6′	9′	12′	15′	30′	Other	
M. S.	F	64-74	72, 72	76	76	76	78	78(S)	74		
M. M. D.	F	70-80	78	88	88(S)	84	84	84			
L. P.	F	60-72	64	80	76(S)	80	74	72			
A. W.	F	66-78	73		74	87(S)		84	80		
W. S. C.	M	46-62	62	94	90(S)	90	88	85			
J. B.	M	68-78	78		92(S)						
A. R.	M	70-84	76, 76	80	84(S)			90	90		
A. K.	M	68-76	72	86	82	82	82	82(S)			
E. A. C.	M	69-81	85, 85		119	108(S)			40′/82		
B. S.	M	68-84	82, 84	Cold empty tobacco pipe in mouth		104(S)			40′/90		
J. C.	M	49-64	57, 64				30′/74	60′/76	90′/74 (S)		
Dr. J.	M	58-62	60					72	70	60′/68 (S)	
E. C. R.	F	69	79	4′/90 (S)				79			
Mrs. S.	F	70-76	72		5′/100 (S)			92	90		
F. M.	F	66-74	66	stopped smoking	15′/—	20′/82	30′/76	60′/70			
M. A.	F	58-73	71		5′/92 (S)						
M. O. N.	F	Min. =64	80	2′/92	5′/98 (S)				80		
G. M.	M	66-76	74	1′/80	3′/78	6′/78	9′/80 (S)	12′/72	15′/72		
M. M.	F	60-72	72	1′/90	3′/92 (S)	6′/86	9′/86	12′/78	15′/80	18′/76	21′/74 24′/72

S = Stopped smoking

Not included in this list are two persons known to be clinically sensitive to cigarette smoke in whom the smoking test was not done.

D. Clark's case and the case of J. K. (epileptic) are also not included.

vomiting and diarrhea. Pulse at first increased, then irregular. Subsequent depression."*

Three of these symptoms may also be toxic, namely, nausea, vomiting,

*Slightly altered from Torald Sollmann's *Manual of Pharmacology*, fifth edition, p. 393, describing the effects of poisoning with pure nicotine on man.

TABLE II. PULSE RECORDS OF SMOKING TESTS IN CIGARETTE-INSENSITIVE PERSONS

	Sex	Normal Pulse Range	Rate Before Smoking	Rate at Intervals After Starting Smoking Time in Minutes					
				3′	6′	9′	12′	15′	30′
C. W. C.	M	61-69	(1) 64 (2) 61	65 61	66 68	66 66	66 64	62 (S) 62 (S)	
L. B.	F	58-70	70, 60	60	69	66	65 (S)	65	
S. I. H.	M	68-80	72	72	72	72	72	72 (S)	
Dr. W.	M		74		74	74		76	74 (S)
D. F.	M	58-68	72	72	72	72	68	68 (S)	
R. S.	F	42-56 (?)	47, 45	45	44	43	43	43 (S)	
W. S. C. Jr.	M		66	66	67 (S)	67	65	68	
M. C.	F		62	60	56	56	58	62 (S)	
D. J.	M	70-76	72, 74	76	76	76	76	76 (S)	
R. La T.	M		68	68	68	68	68	68 (S)	
H. H.	F	60-66	(1) 66 (2) 64	66	Smoking one hour (64-66) 66	64	66	64	66 (S)
Dr. S.	F	66-76	74	74	66	66	70	74 (S)	inhaled
F. S.	M	72-84	84	84	84	84	84	84 (S)	
Mrs. J.	F	68-76	(1) 76 (2) 76	76 76	76 76	78 (S) 76 (S)			
Dr. R.	M	70-76	76, 72	30′ 74	60′ 74	90′ 72	continuous smoking		
M. P.	F	59-72	60, 59	3′ 59	6′ 60	9′ 59		14′ 60 (S)	25′ 62
E. B.	F	72-76	82	3′ 82				60′ 82	20′ 82 (S)
R. K. P.	M	51-61	56		5′ 57	15′ 57	30′ 55	45′ 57	75′ 54 (S)
A. S.	F	70-76	70	3′ 66	10′ 66	15′ 68	24′ 70	35′ 70 (S)	

S = Stopped smoking.

and diarrhea, since they are observed in presumably nonallergic lower animals.

The observations described in the present writing make it seem rather likely that the symptoms observed following smoking in some persons are usually allergic rather than toxic. Certainly no pharmacologist would attempt to explain on a nonspecific, toxic basis the occurrence of epileptic seizures in one person, constipation without headache in another, and in still another, severe headaches without constipation, all proved to have been caused by smoking.

Against an explanation of these symptoms on a toxic basis speaks also the fact that in about half of the individuals *tested* and reported in this article the pulse-rate was not perceptibly affected by smoking and that

symptoms were experienced by only a small fraction of the entire group studied.

In animals toxic doses of nicotine do not exhibit such great variation.

The foregoing considerations, together with the demonstrated significance of allergic tachycardia, justify the separation of the two groups of persons in the tables.

In Tables I and II are listed, respectively, cigarette-sensitive and cigarette-insensitive persons, all individuals of both groups having been identified as subjects of idioblaptic allergy. It is noteworthy that in both groups the two sexes are about equally represented. Nearly all of the subjects had been relieved of their allergic symptoms through the pulse-controlled dietary analysis. Hence, the tests of the effect of cigarette smoking were in each instance carried out by persons having a long experience of numerous daily pulse-counts and a dependably exact acquaintance with the normal and the abnormal variations of their pulse rate.

This consideration alone justifies the interpretation of the pulse-record of G.M. as indicating a specific allergic reaction to the cigarette smoke, although the maximal rate was only 4 beats above his normal maximum. However, this subject had been for some time aware of a distinct clinical sensitivity to tobacco smoke (nausea, acute conjunctivitis).

In my monograph[3], on pages 86 and 87, I have discussed briefly the question whether the significant allergic excitant of tobacco may be nicotine. This question seems a reasonable one because of the known instances of severe allergic symptoms caused by other alkaloids (quinine, morphine). I mentioned also the case of a colleague who experienced unpleasant symptoms when smoking ordinary tobacco but not when smoking "denicotinized" (Sano) tobacco. I am indebted to that colleague, Dr. Guy W. Clark, for the following history of his case and the record of his pulse-counts in the several tests of ordinary and Sano tobacco.

The patient, a man aged fifty-nine, has never had hives or heartburn. He has had evidence of indigestion manifested by gas formation and the frequent appearance of canker sores, but he has had no "nervous sensation," neuralgia, hayfever, asthma or any other signs of food allergies except occasional dizziness when smoking ordinary tobacco. Patient inclined to be underweight but very active in outdoor occupation. He has been an off-and-on smoker from age twenty to forty. For the last twenty years has smoked quite regularly but never to excess, twelve to fourteen cigarettes per day maximum.

In 1939 he experienced an angina-like pain and was examined by a well-known cardiologist who found no organic defects. From the patient's description of his troubles (tachycardia, frequent pain in the left side and excessive gas formation), the physician advised him to stop smoking for a while and see if any benefits were noticed. Being a pharmacologist and quite familiar with drug action, the patient, feeling that the moderate smoking could not be the cause of the trouble, declined to follow the advice of the physician and continued smoking.

In 1942 because of excessive gas formation, the patient consulted an eminent gastroenterologist in Chicago, and after a complete examination, including x-ray of the entire intestinal tract, the advice again was to stop smoking. While discussing the

situation with another physician in New York City, it was suggested that "denicotinized" cigarettes be substituted for the regular brand which had been used. The patient has now used "denicotinized" tobacco mostly as cigarettes but also in pipe-tobacco for more than three years and has been entirely free from the cardiac symptoms and practically free from any signs of indigestion.

While recovering from an eye operation last spring, the patient decided to stop all smoking; this as on previous similar occasions, was followed by some improvement in appetite. This patient has always had low blood pressure, 110 to 120 systolic, and a customarily slow pulse rate, 60 to 66.

Experiment

Pulse Rate

Dec. 16—6:00 P.M.—60 (before dinner)
62
6:25 P.M.—68 (right after first puff of "denicotinized" cigarette)
6:30 P.M.—78
6:35 P.M.—80 (end of cigarette)
8:45 P.M.—62
64
Dec. 18—2:40 P.M.—68 (soon after using tuamine inhaler)
70
2:44 P.M.—70 (repeated tuamine, both nostrils)
2:45 P.M.—74
2:46 P.M.—76
3:05 P.M.—66
3:08 P.M.—66 (lighted standard brand of cigarette, long)
3:10 P.M.—86
3:15 P.M.—90
3:20 P.M.—84 (end of cigarette)
6:00 P.M.—60 (before dinner)
62
6:45 P.M.—64 (right after dinner
7:00 P.M.—68
7:25 P.M.—64
7:30 P.M. (lighted "denicotinized" cigarette)
7:32 P.M.—74
7:35 P.M.—74
7:37 P.M.—76 (end of cigarette)
7:40 P.M.—78

Dr. Clark's experiment, as he says, does not prove the allergic excitant to be nicotine; it does not even indicate that there is not more than one allergen in the usual smoking forms of tobacco. However, it leaves no doubt that the partly denicotinized tobacco is, whether for a qualitative or a quantitative difference, distinctly less allergenic than ordinary tobacco.

It is, of course, conceivable that subjects more allergic to the cigarette allergen would not experience the differences between the two products that are reported by Dr. Clark. With the expression "more allergic" I am referring to shock-organs, particularly the renal, that may be affected by lesser concentrations of the tobacco allergen and which are not involved in Dr. Clark's case.

SUMMARY

1. Reaginic sensitivity to tobacco affects only a small percentage of the population (about 1 per cent according to Aaron Brown). Symp-

toms proved to be due to reaginic sensitivity to tobacco have not been reported.

2. A number of instances of idioblaptic (nonreaginic) sensitivity to cigarette smoke are described in whom different characteristic symptoms were experienced (epileptic seizures, dizziness, headache, constipation, abnormal tiredness, indigestion, "fearfulness," menorrhagia). In all cases the symptoms ceased when smoking was discontinued.

3. With the criterion of specific tachycardia, it has been found that about half of all nonreaginically food-allergic persons of both sexes are allergically sensitive to cigarette smoke.

4. In one case the smoking of partly denicotinized tobacco caused an elimination of the symptoms (dizziness) and a distinct reduction of the tachycardia (two tests) that regularly followed smoking of ordinary tobacco.

ADDENDUM

After I had dispatched the manuscript of this paper, I received a letter from Dr. Clarence W. Lieb, calling my attention to the similar study of Harry L. Segal,‡ in which much of my findings were anticipated, though differently interpreted.

In this study of six patients, whose chief complaint was fatigue (one of the most frequent allergic symptoms), a constant finding was marked acceleration of the heartrate, (up to 100 or more in all). The fatigue was "relieved" in all of these persons after cessation of smoking.

Segal is careful to report that "not all patients who are tired and who smoke are improved by discontinuing the smoking." Thus he noticed the limitation of the described relationship to *certain* individuals, yet this specificity did not suggest allergy to him, and after excluding other irritants from consideration, he ascribed the effects to the pharmacologic action of nicotine, which he found effective in some persons in relatively small "dosage."

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INSUFFLATION OF SULFONAMIDE DRUGS

(Continued from Page 433)

the cough would continue to develop in many patients but not in as many as had been formerly observed. The numbers in whom sinusitis and the various forms of otitis developed were definitely lessened when compared with the numbers of patients not so treated in whom these complications appeared. The greatest value of the insufflation of the powdered sulfonamide compounds appeared to be in the first three or four days of the acute infection. Insufflation of the sulfonamide compounds proved to be as safe as their oral use. Only seven out of the 1,500 treated gave evidence of sensitivity as manifested by dermatitis, hives or hay fever-like symptoms.

THE USE OF SEX HORMONES IN ALLERGIC DISORDERS

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WHILE obtaining the initial history of a female patient with an allergic disorder, the physician may unearth a tendency to exacerbation or onset of symptoms during the premenstrual phase or during actual menstruation. After the proper elimination and desensitization measures are instituted, such a tendency may still be apparent, although to a lesser degree. Patients who previously were ill throughout the entire cycle may now be consistently affected only during one phase of it. Several months of observation while under standard allergic management may be necessary to establish these facts. Keeping combined menstrual and symptom calendars is a worth-while procedure, for without such a permanent record valuable information may be overlooked.

The adolescent girl may lose or may start clinical manifestations of allergy at puberty; exacerbation of previous difficulties at this time is common. Quite frequently women whose allergic disorders have been well controlled may have marked exacerbations at the climacteric. Both the loss and the acquisition of allergic disorders are commonly noted at the menopause.

Pregnancy may exert either a beneficial or an adverse effect on the course of allergy. Indeed, it is the author's experience that it is more likely to follow one of these courses than to leave the allergic state unaffected. Pregnancy gives rise to disorders peculiar only to the gravid state; in latter years there has even been a suspicion that the early toxemias of pregnancy may be due to an endogenous hormone allergy.[6,7,29]

All of these repeatedly observed phenomena obviously must have some relation to ovarian and anterior-pituitary gland function. Study of the normal pattern of female pituitary and sex hormone physiology and of the deviations found in the cases under discussion yields information not only interesting but therapeutically useful. Rational hormone therapy to aid specific allergy management is the welcome result.

ENDOCRINE DYSFUNCTION AND ALLERGIC MANIFESTATIONS

That specific sensitivities, important as it is to known them, are not the only factors concerned in the production of allergic manifestations is well known. Why a given allergen can at one time provoke a clinical manifestation of allergy and at other times not is determined by other factors which modify the allergic balance. Dysfunction of the autonomic nervous system, infections, the emotional state, and endocrine dysfunctions are among the most important factors.

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Endocrine dysfunction may bring about clinical manifestations of allergy in any one or more of the following ways:

(a) By affecting the balance of the autonomic nervous system toward a parasympathetic preponderance.

(b) By affecting the emotional state of the individual so that he is more labile psychosomatically.

(c) By lowering his resistance to infections, which usually cause exacerbations of clinical allergy.

(d) By disturbing the allergic balance through excess or deficiency of specific hormones, or through hormonal imbalance.

(e) By primary allergy to endogenous endocrine products.[38]

(f) By the possibility of anti-hormones to gonadotropins administered therapeutically causing secondary reactions.[34]

RECOMMENDED METHODS FOR QUANTITATIVE HORMONE STUDIES

It is obvious that quantitative measurements of the various ovarian and pituitary hormones in the blood or urine are necessary for the diagnosis of obscure cases and advisable in the seemingly obvious ones. Unfortunately, all of the tests are characterized by being rather complex and time-consuming. Out of the large number available, the author prefers the following four:

(1) Fluhmann's test for thylakentrin in blood;[8,9,11]

(2) The vaginal mucification method of Fluhmann for blood estrogen;[10]

(3) The Venning-Browne gravimetric test for sodium pregnanediol glycuronide (an excretion product of progesterone) in the urine;[36]

(4) Callow's colorimetric method for estimating urinary androgens.[2]

The Fluhmann FSH or thylakentrin test deserves special mention; it requires at least 50 mouse units FSH per liter of blood to produce a positive test. It is usually positive in primary ovarian failure and negative in normal mature women. A positive test with a negative estrogen test denotes primary ovarian failure,[11] as in the climacteric. A negative reaction with a positive estrogen test indicates a responsive ovary, and a negative test along with a negative estrogen test indicates ovarian depression secondary to pituitary hypofunction.

MODERN CONCEPTS OF FEMALE ENDOCRINOLOGY

During childhood there are minute amounts of estrogen, androgen, and follicle-stimulating hormone of the anterior pituitary (FSH) (thylakentrin) in the circulation and no progesterone. At puberty there is an increase in thylakentrin and a resulting general stimulation of the primordial follicles of the ovaries to produce estradiol. Under the influence of estradiol, which is present in appreciable but variable concentration until

the climacteric, the secondary sexual characteristics develop and are maintained in their integrity. The first menstruations are anovulatory in most cases, endometrial degeneration and bleeding being due to fluctuations in estrogen production.[27] Rise in blood estrogen beyond a certain point depresses anterior pituitary function;[28,35] this in turn diminishes the stimulus to estrogen production. While under the influence of adequate estrogen, the endometrium goes through the proliferative phase, and when estrogen with its stimulus is withdrawn degeneration takes place.[27]

After a variable period of such cyclic bleeding or anovulatory menstruation, the adult ovulatory type of menstruation appears. During active menstruation, blood estrogen is at its lowest levels, and thylakentrin from the uninhibited anterior pituitary causes the growth of a primordial ovarian follicle and secretion of estradiol by its theca and granulosa cells during the postmenstrual and preovulatory periods. Endometrial repair and growth proceed under the influence of estradiol, and the follicle enlarges. At the time of ovulation the follicle ruptures, and there is a drop in blood estrogen content, following which there is occasionally a short period of intermenstrual bleeding. The organization of the corpus hemorrhagicum into the corpus luteum and secretion of progesterone is due to the influence of the luteinizing hormone of the anterior pituitary (LH) (metakentrin), which started its appearance just prior to ovulation. The corpus luteum is maintained in an active state for the production of progesterone by the lactogenic hormone (prolactin) of the anterior pituitary.[5]

Following the ovulatory phase drop, the concentration of estrogen again increases until the twenty-second day of the cycle, which is about the peak of progesterone concentration also. There is then a drop in the concentration of both, most rapid on the twenty-sixth day, due presumably to failure of stimulation from the reciprocally inhibited pituitary with consequent degeneration of the corpus luteum. Normal menstruation then follows on the twenty-eighth day, estrogen is at its lowest, and the uninhibited pituitary repeats the cycle.

If conception and implantation take place, the premenstrual drop does not occur. Instead, blood estrogen and progesterone increase, and chorionic gonadotropin appears. Chorionic estrogen and progesterone appear later. After parturition, chorionic hormones and progesterone disappear, estrogen levels drop, and the pituitary-ovarian cycle is resumed.

At the climacteric, the ovary is no longer responsive to thylakentrin stimulation with the growth of a follicle and production of estrogen. The climacteric phenomena can be ascribed to (a) an increased production of follicle-stimulating hormone from the uninhibited anterior pituitary or (b) a lack of estrogen. The evidence favors the former view, as inhibition by other means, such as testosterone, can relieve menopausal symptoms.[31] Occasionally, too, there are instances in which there may be some increase in blood estrogen following the cessation of menstruation.

The steroid hormones of the adrenal cortex are closely related chemically to the gonadal steroids and have some estrogenic properties, although it has been said that their androgenic effect may indirectly influence ovarian function. Certainly, the adrenal steroids may produce changes in the sex organs of either sex. The androgens may possess estrogenic[4] and progestational[23] qualities, and progesterone may have slight androgenic activity. To help complicate matters, estrin and progestin occur in the adrenals.[3] Since the female physiologic sex pattern, normal or abnormal, depends on the hormonal balance operating at the moment, and since the net effects can be achieved by various combinations of hormones, it inevitably follows that different authors have different explanations for the same clinical manifestation. The correctness of one explanation casts no reflection on the accuracy of another, since clinical material doubtless can be found to corroborate each.

PATHOLOGICAL ENDOCRINE PHYSIOLOGY AFFECTING THE ALLERGIC STATE

1. Hormonal patterns during puberty when not producing the usual anovulatory type of menstruation are characterized by their irregularity and unpredictability from month to month. Spontaneous adoption of a characteristic pattern is only a matter of time. The effect on the emotional state is the significant factor.

2. The patients with "premenstrual" allergic disorders are those with premenstrual tension or the milder grades designated as premenstrual distress. In the classical case of premenstrual tension the patient exhibits nausea, headache, fever, nervous tension, lower abdominal pains and back pains. These symptoms come on five to seven days before the onset of the period and end when menstruation begins. Blood estrogen determinations have shown that patients suffer from too much estrogen,[12,22] and no thylakentrin is demonstrable. The postovulatory or premenstrual blood estrogen concentration rises to a height which produces toxic manifestations, or, as Zondek has shown, these patients are "allergic" to their own endocrine products.[38] The ovarian steroids cause sodium retention and extracellular edema; in the brain this leads to headaches, in the skin to pruritus and urticaria, and in the gastrointestinal tract to distention, disordered peristalsis and vomiting.[16]

When the "premenstrual" group is tested intradermally with estradiol or estrone in oil (0.1 mg. in 0.1 c.c. oil) with a simultaneous oil control, a positive skin test is usually obtained. It is either papular or erythematous, usually coming on in three to five hours and persisting for at least a day. A passive transfer test with the premenstrual serum of a "premenstrual type" patient to a normal woman will give a positive test with estradiol, but the normal recipient's untreated site will not react to estradiol. The direct test could be interpreted as an index of the patient's tissue susceptibility to the irritant effect of estrogen rather than as an

index of allergy to it. The passive transfer test, however, could only have the latter significance.

The allergic difficulties of patients with premenstrual tension are aggravated by the high estrogen levels of pregnancy but end at the menopause.

3. The patients of the true "menstrual" type usually do not experience the onset or exacerbation of their allergic difficulties until the first day or two of menstruation, but occasionally may on the day before. There is ordinarily more or less nervousness, irritability, dysmenorrhoea, and abnormality of flow. Little or no fever is the rule. There is no increase in blood thylakentrin concentration, and blood estrogen levels are low. In this group neither the direct estradiol "sensitivity" test during the premenstrual or menstrual phase nor the passive transfer test with the premenstrual serum can be elicited. They are likely to improve during pregnancy but often change over to the "menopausal type" at the climacteric.

4. As previously stated, the high estrogen levels characteristic of pregnancy may be beneficial to the patient of the "menstrual" type who becomes pregnant and be detrimental to one in the "premenstrual" group. The abundant estrogen has been exonerated as a cause of the early toxemias of pregnancy, but other hormones of pituitary and ovarian origin are still suspect.[6,7,29]

The ovary's production of estrogen may be diminished by pituitary inhibition with testosterone, but the placental production is unaffected.[17] The same experiments can be interpreted to mean that estrogen of ovarian origin is neutralizable physiologically by testosterone, but estrogen of placental origin is not.

5. Although both increased blood thylakentrin levels and decreased blood estrogen levels are found in the climacteric, it is the former condition which is characteristic. The estrogen is usually absent or low, but occasionally may be increased (possible extra-ovarian source?). When high, there is likely to be menorrhagia.

RATIONAL THERAPY OF PITUITARY-OVARIAN DYSFUNCTION AFFECTING THE ALLERGIC STATE

"Puberty Type"—No hormonal therapy is indicated because there is no consistent hormonal pattern to modify. In the majority of cases the endocrine factor responsible for the production of allergic manifestations will disappear during the normal course of maturation. Only psychotherapy plus the usual allergic management is indicated.

"Premenstrual Type"—Restriction of sodium chloride and administration of ammonium chloride provide more or less control of the characteristic sodium retention and extracellular edema.[16] There is partial prevention of the effects of the excessive estrogen, but nothing is done toward neutralizing the estrogen or inhibiting its production. Results, when obtained, are rarely complete.

The use of progesterone, under the supposition that premenstrual tension was due to unantagonized estrogen consequent to deficient luteinization,[22] has not produced any spectacular results in the author's hands.

The observation that Vitamin B deficiency impaired the liver's ability to detoxify estrogen[1] with consequent high blood estrogen levels led to the use of Vitamin B complex for premenstrual tension. The author's observations in allergic individuals with premenstrual tension is that the effect is likely to be spectacular if there are clinical signs of vitamin deficiency present but will be equivocal otherwise.

Excellent results were obtained by the author with the administration of 10 mg. of methyl testosterone orally twice daily for ten days before the onset of the expected period. The male hormone depresses the anterior pituitary function, which in turn results in less production of estrogen by the ovary; a direct antagonism of androgen and estrogen is also a possibility.[32] When employing this mode of therapy, it is advisable to withhold it every fourth month to note progress.

Another promising treatment in the author's hands is the subcutaneous or intramuscular (latter preferred) "desensitization" to alpha estradiol compounds starting with the amount just failing to give a positive skin test. Succeeding doses ascending by geometric progression are given every two or three days until tolerance is reached. Whether this should be considered as a form of classical desensitization or merely physiological adaptation to increased estrogen levels is a moot point.

It is of interest to note that urticarial attacks occurring during the premenstrual period can be duplicated in the inter-menstruum by injecting serum taken during the premenstrual period.[15] This would point either to a specific hormone or a specific allergen present at the time as the cause of the symptoms. Treatment with premenstrual serum has not worked well.

"Menstrual Type"—The physiological preventative is a large dose of estrogen so timed as to prevent or buffer the exaggerated drop in blood estrogen just before and during the menstrual phase. Because timing is so important and oral absorption so erratic, a single intramuscular dose of estrogen, preferably one of the "natural" or estradiol series, is used. The author has found that it usually requires a dose of 1 to 2 mg. of estradiol dipropionate or benzoate administered two to four days before the estimated onset of the period. It is advisable to withhold such therapy every fourth month in order to note any tendency toward spontaneous improvement.

"Menopausal Type."—Here the indication is for the administration of estrogen by oral or parenteral route in amounts adequate enough to inhibit the anterior pituitary function and then gradually tapering off.

Initially, there is a tremendous variation in dosage. By the intramuscular route, for example, between 5,000 and 50,000 international units may be required two or three times weekly at the outset. The vagaries of the percutaneous and vaginal routes of administration render them unsatisfactory.

If menorrhagia is present without changes requiring surgery or radiation, one may use androgen to inhibit the anterior pituitary function and stop the bleeding.

During the menacme, in addition to the premenstrual and menstrual types of migraine, there is a type of migraine associated with spasmodic excess thylakentrin production. In spite of its occurrence in youth, its similarity to the menopausal type is striking. This type is preceded by a rise in gonadotropin in the urine followed by a drop on the first day of the seizure, and with little or no estrogen demonstrable.[30] In the majority, an injection of human chorionic gonadotropin will precipitate an attack. This kind of headache can occur at any time during the cycle, and these patients usually have similar headaches after the menacme. The climacteric may even aggravate the condition. It is the author's impression that these headaches are more likely to occur during mid-cycle, the only time that thylakentrin is ordinarily demonstrable in the blood and urine.[13] Estrogen therapy,[33] though logical, has not been completely satisfactory because of the obvious difficulty of timing. Continuous estrogen therapy would be illogical and possibly harmful.

"Pregnancy."—The relief afforded those patients of the "menstrual type" is gratefully accepted. Although the "premenstrual type" is aggravated by pregnancy, hormonal therapy is rarely indicated. Progesterone therapy, salt restriction, and Vitamin B therapy employed for such complications as toxemias, habitual abortion and threatened abortion can effect allergic manifestations if the patient is basically one of the "premenstrual" type. The successful use of testosterone therapy to inhibit the rate of production of skin pigment due to estrogen excess[17] suggests its cautious trial in severe allergic conditions with the same basis occurring during pregnancy.

RESULTS OF THERAPY

The effects of pituitary-ovarian dysfunction are most notable in migraine, urticaria and asthma, less visible in perennial allergic rhinitis, and hardly noticeable in seasonal allergic rhinitis and eczema. Patients with the last two disorders were not included in this study. Table I presents cases classified under allergic disorders. Table II regroups the same cases from the standpoint of endocrine dysfunction.

ALLERGY TO VEHICLES

The possibility that patients may be allergic to the oily vehicles used in parenteral preparations of androgens and estrogens must be con-

TABLE I.

Allergic Disorder and Subtype	Total Cases	Number Improved	Therapy Employed	Remarks
URTICARIA				
Menopausal	20	17	Estrogen in 18. Androgen in 2	(a)
Menstrual	19	17	Timed estrogen parenterally	
Premenstrual	9	3	Vitamin B Complex	(b)
Premenstrual	12	11	Methyl testosterone orally	
Premenstrual	10	7	Estradiol "desensitization"	
78% Improved	70	55		
MIGRAINE				
Menopausal	18	14	Estrogen	
Menstrual	14	12	Timed estrogen parenterally	
Premenstrual	11	4	Vitamin B Complex	(c)
Premenstrual	7	7	Methyl testosterone orally	(d)
Premenstrual	3	3	Estradiol "desensitization"	(e)
75% Improved	53	40		
ASTHMA				
Menopausal	24	22	Estrogen	
Menstrual	14	11	Timed estrogen parenterally	
Premenstrual	7	4	Methyl testosterone orally	(f)
Premenstrual	7	5	Estradiol "desensitization"	(g)
81% Improved	52	42		
PERENNIAL ALLERGIC RHINITIS				
Menopausal	16	13	Estrogen	
Menstrual	7	5	Timed estrogen parenterally	
Premenstrual	2	2	Methyl testosterone orally	
80% Improved	25	20		

(a) Two patients with menorrhagia treated with testosterone.
(b) No obvious clinical avitaminosis.
(c) Clinically avitaminotic.
(d) No obvious clinical avitaminosis. Had preceding treatment with Vitamin B Complex without results.
(e) Also had urticaria.
(f) Negative Estradiol skin test.
(g) Positive Estradiol skin test.

TABLE II.

Type	Total Cases	Number Improved
MENOPAUSAL		
Urticaria	20	17
Migraine	18	14
Asthma	24	22
Perennial Allergic Rhinitis	16	13
84% Improved	78	66
MENSTRUAL		
Urticaria	19	17
Migraine	14	12
Asthma	14	11
Perennial Allergic Rhinitis	7	5
83% Improved	54	45
PREMENSTRUAL		
Urticaria	31	21
Migraine	21	14
Asthma	14	9
Perennial Allergic Rhinitis	2	2
67% Improved	68	46

sidered.[25] Peanut and cottonseed oils, commonly used for this purpose, are well-known allergens. Sesame, corn and olive oil allergies are much less frequent but do occur. Certainly, the possibility of allergy to the vehicle (about 4 per cent of women) should be considered before the

possibility of hormone allergy, and proper control tests made. Oral therapy or the parenteral use of aqueous suspensions are indicated in this vehicle-sensitive group.

PRECAUTIONS IN ENDOCRINE THERAPY

It would not be wise to close this paper on sex hormone therapy without mentioning some required precautions and the reasons therefor. Sex hormone therapy should not be employed unless there are definite indications and the clinical condition is of appreciable severity. A history of neoplastic disease or tendency thereto in the patient and her blood relatives should be obtained and carefully weighed. Examination of the pelvic organs and breasts in women should be performed before commencing endocrine therapy and should be repeated at appropriate intervals. Uncontrolled androgen therapy in women can lead to hirsutism, voice changes and menstrual changes. Protracted estrogen stimulation plays a part in the etiology and growth of uterine fibroids,[26,37] endometriomata,[24] cervical neoplasms[14] and uterine carcinomata.[19,21] The incidence of breast carcinoma is believed to be increased by prolonged estrogen stimulation.[18,20] In experimental animals, prolonged high-dosage estrogen treatment results in pituitary changes, characterized by the complete degranulation of the basophile cells, subtotal degranulation of the acidophile cells, and the formation of large chromophobic adenomata.

SUMMARY AND CONCLUSIONS

Allergic phenomena frequently cease or begin at puberty or the climacteric, and during the menacme they may be exacerbated during the menstrual or premenstrual period. At these times the usually satisfactory allergy regimes of elimination and desensitization may be relatively ineffective. The ways in which endocrine dysfunction may bring about clinical manifestations of allergy are listed. The aberrancies in pituitary-ovarian function in the groups of allergic patients under discussion are analyzed. Important factors determining the type of sex hormone therapy are: the time of appearance of clinical manifestations; the gonadotropic and steroid hormone inventory at that time; the presence of endogenous hormone sensitivity.

In general, allergies appearing at puberty should receive the usual allergy regime plus psychotherapy for the disturbed emotional state until some consistent hormone pattern is established. Menopausal onset or exacerbation is due to uninhibited pituitary overactivity, which may be inhibited by estrogen but also by androgen if bleeding is present. Satisfactory results were obtained in 84 per cent of this group. Menstrual phenomena are usually due to transient estrogen deficiency, which can be prevented in 83 per cent of cases by a single large properly timed injection of estrogen just before the expected period. Premenstrual exacerbations or appearances are usually associated with "premenstrual tension," the fundamental

difficulty being temporary estrogen excess with altered reactivity to same. This can be combated by oral methyl testosterone therapy during the postovulatory and premenstrual phase or by "desensitization" to estradiol, skin sensitivity to which can be demonstrated. Sixty-seven per cent of the "premenstrual" group responded satisfactorily to therapy.

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MOLD FUNGI: MOLD EXTRACTS

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LIGHT URTICARIA

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IT was Bazin[5] in 1855 who first called attention to the fact that sunlight, acting on a sensitive skin, can produce various types and degrees of reactions to it. Then came Anderson[2] who first introduced the thought that a photosensitizing substance might play a role in such cases. Later Duke[15] described illnesses, caused by sensitiveness to the action of physical agents, e.g., light, heat, cold, and mechanical irritation, as cases of "physical allergy." He mentioned two distinct varieties of physical allergy. In one type, the reaction is confined to the skin area directly exposed to the physical agent (called contact reaction); in the other type, the reaction may involve not only the skin areas directly exposed, but also distant tissues as well (called reflex-like reaction). He considered the contact type as comparable to the drug allergies, while the reflex type was regarded as probably caused by a disturbance of the heat-regulating mechanism of the body. It was Duke who called especial attention to the physical agents as causes of many cases of urticaria and angioneurotic edema, and sometimes also of such conditions as asthma, coryza, headaches and tachycardia.

The question as to whether sunlight urticaria is a genuine allergy, or whether it is only a photodynamic phenomenon has been discussed by many authors. Entering into this discussion has been the reported successful passive transfers with their implications of a true allergy.

The passive transfer of photogenous urticaria has raised the question of whether only reagins are transferred in the serum, which enters the cells of the test person, and become activated under the influence of the homologous light (a genuine allergy); or whether there is a transfer of an already known photosensitizing substance becoming active likewise under the influence of light (a photodynamic phenomenon). The theoretic difference between the two concepts consists in the fact that for the allergic theory, it presumes a reagin, put into action by the light and inducing urticaria through forming H-like substances. In contradistinction, a photodynamic chemical, e.g., porphyrin, et cetera, may be the photosensitized substance transferred, according to the latter concept. In this vein of thought, Rajka[23] believes that positive passive transfer is only possible in a specially strong hypersensitivity, i.e., at a high reagin titer of the blood, when the reagins, fixed in the cells, enter the circulation in an appreciable quantity.

In support of the first theory Sulzberger and Baer[24] obtained a positive passive transfer, and ascribed the urticarial sensitivity as due to the presence of an antibody (reagin) in the blood stream. They argued this point on the fact that (1) incubation of their patient's serum for one

hour at 60° C. abolished the capacity of the serum to transfer the light hypersensitivity to normal skin; (2) one full reaction-producing exposure of a passively sensitized site sufficed to exhaust its capacity to react; (3) no known photodynamic nor photosensitizing chemicals (porphyrins, et cetera) were demonstrable in their patient's serum; and (4) if not exposed, the sites of serum depot did not diminish in sensitivity to light, but gave maximum reactions four days or more after their injection into normal skin. For these reasons, they believed in the presence of an antibody (reagin) here.

Contrariwise, Epstein[16,17] emphasizes that while passive transfer in the sense of the Prausnitz Kustner phenomenon is always an expression of allergy, yet, in dermatoses due to hypersensitivity to light, the term passive transfer has been used in a wider sense indicating any form of transfer of such hypersensitivity from one person to another. This transfer, he stresses, does not necessarily imply allergy. A photosensitizing agent causing the patient's hypersensitivity to light may be present in his serum and in this way, account for the reaction on the part of the recipient. Such a mechanism, he believes, seems indicated in Callaway's[13] first positive passive transfer reported in this country. Another point Epstein makes is concerning the antigen itself. Ordinarily, in the Prausnitz Kustner phenomenon, antibodies from the patient's serum are transmitted to the test person. The positive reaction is elicited by subsequent injection of the antigen into the prepared site of the recipient. The mechanism of passive transfer in the photoallergic condition is the same in principle. The antibodies are transmitted with the donor's serum. Yet there is this difference. The antigen is not injected but must be produced at the recipient's site by the action of light upon the proantigen, and the latter must have been transmitted with the donor's serum.

Blum et al[11] in their case of a positive passive transfer demonstrated that the light absorber, which is constantly present in the patient's skin, and the light absorbers in the area of normal skin, photosensitized by passive transfer, have the same action spectra; and are therefore presumably identical. The wheals, too, are produced in the areas of passive transfer by the same wave lengths that elicit the urticarial response in the light-sensitive patient.

The various parts of skin of the body exposed to light have a definite effect on reactions produced by light, in these light-sensitive cases. Thus, Blum[8] showed by measuring the threshold times of various portions of the body, that their skin photosensitivity varied. The more exposed areas, e.g., the palm of the hand, the back of the hand and the cheek, were much more insensitive to light than, e.g., the abdomen or the back. In other words, parts of the body habitually exposed are considerably less sensitive than those usually covered by clothing.

The active site of the reaction that develops in photosensitivity, is believed to be close to the minute blood vessels in the papillary layer

of the skin.[8] The "burn" produced by ultraviolet light takes a few hours to appear and the longest wave length that can produce it is about 3150 A°, with a maximum at 2967 A°. Here, the erythema production takes place in the basal cells of the Malpighian layer and in the corium of the skin.[20]

Sir Thomas Lewis[21] demonstrated that the response of cutaneous vessels to mechanical, electrical, thermal or chemical injury is triple. There is (1) reddening due to capillary dilatation, (2) a mottled red flare with crenated edges, the result of arteriolar dilatation and (3) a wheal due to the increased permeability of the minute vessels which permits the escape of fluid in the tissue spares. Histamine produces this typical "triple response" of Lewis. Hence, since the response of the skin, in urticaria solaris, resembles this triple response of Lewis, it is thought the rays of the sun liberate in the skin, histamine or a closely related H-substance.

H. Abramson[1] never found pseudopods develop even in 500 wheals produced as result of exposure to light. Hence, he believes the non-development of pseudopods is not in accord with the theory that a readily diffusible H-substance, like histamine, is liberated in the tissues subsequent to irradiation. He also demonstrated that a histamine wheal may be readily formed (by iontophoresis or injection) over an irradiated area of the skin which has responded, by whealing, to sunlight. In other words, the whealing response to light does not prevent histamine whealing in the same area. Similarly, a light wheal may be superimposed on a wheal formed by histamine iontophoresis. Thus, he argues that a histamine or readily diffusible H-substance is not responsible for the skin response to light irradiation. Duke[14] likewise found no tendency to spread, with pseudopod formation beyond the area exposed to the irritating agent, in his case further argument against the presence of a readily diffusible H-substance.

Contrariwise, Blum, Allington and West[6] noted the marked resemblance of the response of their patient to the triple response of Lewis. Thus, after exposure of the skin to sunlight, an erythema was first produced within a few minutes, limited to the area exposed. After a short time edema appeared, likewise restricted to the exposed area and still later an erythema developed, surrounding and spreading outward from the edematous area. After a few hours, no discoloration nor trace of the occurrence was found. Furthermore, no pigmentation developed. They further demonstrated that this photoresponse does not depend upon the presence of molecular oxygen.

Sulzberger and Baer[24] present the hypothesis that the change produced by light consists of the local conversion of a pre-urticariogenic substance into an urticariogenic substance or the liberation of an urticariogenic substance. This substance, formed or liberated, is nondiffusible, since the effect of irradiation is limited to the irradiated area. They found a

slight rise in the blood histamine level, and concomitantly, a slight rise in the free and total gastric acids, about twenty minutes after exposure to light. These findings suggest that histamine, or a histamine-like substance, is liberated or produced at some stage in the patient's reaction to irradiation.

Laurens[20] does not believe that porphyrins necessarily play a part in light sensitivity, but may represent products of skin injury, and be a result rather than a cause of dermal sensitization. This is stated because it has been noted that while porphyrins may sensitize the skin, e.g., in lead poisoning, porphyrins also have been found to be reduced in some cases of hydroavacciniforme. Also, light sensitivity may even be reduced when porphyrins are present in large quantities, in other cases of hydroavacciniforme. Callaway[13] reported an increase of coproporphyrin I in his case. Urbach and Shay[25] found only a slight increase in the stool and urine output of porphyrin. Anderson and Ayres[3] believe that sulphur metabolism plays a role in the production of light sensitivity. Porphyrins probably play little part in producing lesions of sunlight sensitivity.

In their experiments Blum and West[7] demonstrated that response to light obeys the reciprocity law, i.e., there is a reciprocal relationship between response, and the intensity and duration of irradiation. Also, the reaction which develops is not greatly affected by temperature. All parts of the body were found to be sensitive to light (with the usual variations found in habitually exposed areas, as contrasted to clothing-covered areas). Furthermore, there was not much fluctuation in sensitivity, during the course of ten months' study, showing the influence of time on light sensitivity.

CASE REPORT

The patient first presented herself for study at the age of thirty-five, in the spring of 1942. She gave a history of first developing itching and hives on exposure to sunlight at the age of twenty-five. She had consulted a variety of physicians and taken innumerable prescriptions and used various types of lotions to no effect.

Her previous medical history was completely negative. Menstruation began at the age of thirteen, occurred every twenty-eight days and lasted for three days, and tended to be on the scant side. Patient was always inclined to obesity. Unless she watched her diet carefully, she would gain weight quite rapidly.

At the time of the initial visit, a lotion containing pheynl salicylate, and tannic acid in alcohol was prescribed. No relief was obtained from the lotion. As patient lived out of town it was suggested further studies would be required.

The following year, in 1943, patient was admitted to the Jefferson Hospital for study. Her blood sugar and urea were within normal limits. Wassermann test was negative. Blood proteins were 7.7 mg. of which albumen was 5.6, and globulin 2.1, a normal ratio. The complete blood count and urine studies revealed no abnormality. No eosinophiles were found in the smear. The blood cholestrol was 228 mg. and the basal metabolism rate was minus 20. The free and combined urine estrogens were less than 6, and the combined were less than 5.

Examination of the patient revealed a well-developed woman, on the stoutish side, with no rash present on the body. There was some slight pigmentation

present of the exposed areas of the skin. Eye ground examination was negative, teeth were in good repair, tonsils were out and the thyroid was not enlarged. Heart and lungs were found normal and abdominal examination was negative. There were no aberrant reflexes.

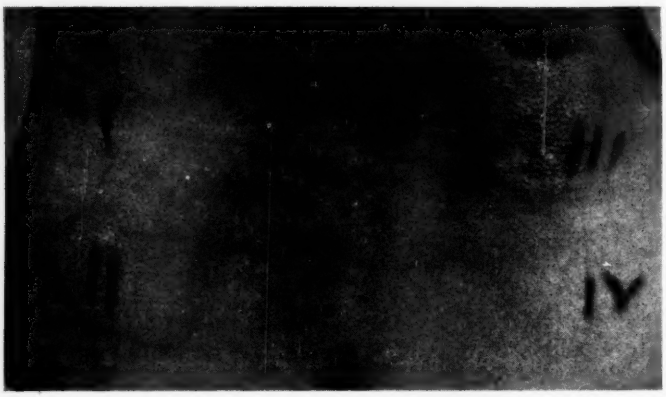

Fig. 1. The patient after exposure to (I) infra-red lamp at 30 inches for ten minutes, (II) hot quartz lamp at 30 inches for two minutes, (III) Kromyer ultraviolet lamp at 1 inch for thirty seconds, and (IV) Tungsten lamp. The photograph was taken about ten minutes after lamp exposures. The same exposures on a control patient, of the same age and hair-coloring, produced no reactions at all.

Exposure of the skin of the forearm to an ordinary summer's day sunlight for three to five minutes produced a hive corresponding in size to the area exposed. Around this would develop an intense red flare. There was no tendency for the hive to spread beyond the area exposed to sunlight, and the line of demarcation was quite sharp. On a summery day, with not too bright sun, it required about eight minutes' exposure to develop urticaria. Exposure to sunlight through ordinary window glass would produce urticaria also, but the time required to induce the reaction was increased by one and one-half to two times and, furthermore, the wheal itself was not as large nor the itching as intense as when no glass filtered the sunlight. Ordinary window glass, of the type that filters out rays below approximately 3200 A° was used. Gradually, the wheal and erythema faded and left no trace of its previous existence.

According to her history, this patient developed sunlight urticaria even in winter, although the symptoms were quite mild and a longer exposure was required. Blum et al[9] noted that where the urticarial response is elicited by a much larger fraction of sunlight, the patient suffers even in winter. The winter sunlight, while it does not contain as great a fraction of the sunburn-producing radiation rays as summer sunlight, does have waves that elicit an urticarial response almost as much as summer sunlight.

A fluorescent lamp failed to produce any erythema or urticaria in our patient. Blum[12] found that his patient developed some erythema, but no whealing as a result of exposure to fluorescent lighting.

Exposure to tungsten lamp, carbon-arc lamp, infra-red lamp, and x-ray failed to induce any reaction in the patient. Thirty seconds exposure to a Kromyer ultraviolet lamp at 1-inch distance (without filter) produced a prompt reaction in the patient within two and one-half minutes with development of a hive and erythema.

Exposure to a hot quartz lamp for one minute at 30 inches produced a hive with erythema within three to three and one-half minutes (Fig. 1). Exposure of a control patient to the same lamps produced no reaction.

Intradermal skin tests were performed, and these proved essentially negative

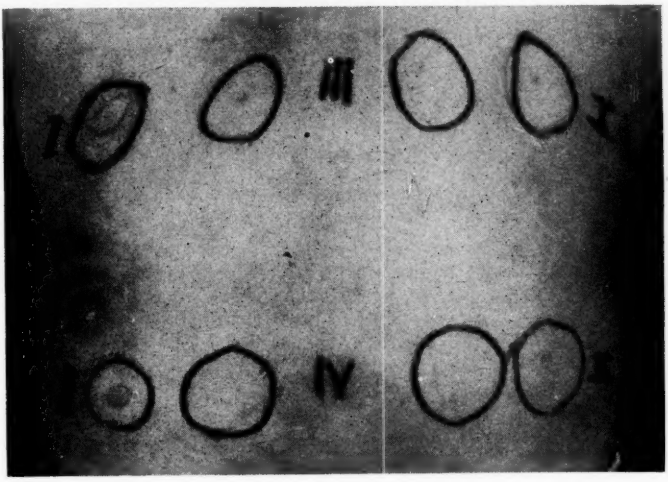

Fig. 2. Passive transfer in the control patient. On the left side of the spinal column are four sites prepared from serum of the sunlight-sensitive patient. On the right side are four similar sites prepared from serum of a nonsensitive donor. Sites I and II on the left responded to the Kromyer and quartz lamps, respectively, with the Kromyer giving the better reaction. There was no reaction in sites III and IV after exposure to infra-red and tungsten lamps, respectively. The sites on the right side, passively sensitized with normal serum, naturally showed no reaction to any of the lamps.

with the exception of moderate reactions to buckwheat, barley, and wheat. The patient stated that ingestion of cereals seemed to make her feet swell.

Estrogen in doses of 10,000 international units, three times weekly, along with thyroid extract, grains 3 daily, and a diet, low in fats, and cereal free, were prescribed.

The patient left the hospital and during the rest of the summer (July and August) continued her treatment with no relief.

In 1944, late in the winter, she began limited exposures to sunlight, first covering her skin with mineral oil, and continued this practice into the summer. She attained quite a tan that summer but despite this, failed to obtain more than slight relief. We know that pigmentation fails to protect these patients from their urticarial reaction the way it protects people from sunburn.

Urticaria solaris is not followed by pigmentation, and it is independent of oxygen.

At one point of her treatment, the patient, believing that her deep tan would protect her, lay on a seashore beach for half an hour in a bathing suit. She promptly lapsed into complete unconsciousness. Efficient treatment with large doses of adrenalin, and external warmth, revived her after a few hours.

In the spring of 1946, the patient was seen again, with a history of brief unconsciousness, as a result of fifteen to twenty minutes' exposure to the Florida sun. The patient had tried using a Hanovia sun lamp in increasing amounts, starting with very brief exposure, in an effort to build up her tolerance to sunlight. This

too had failed. A series of histamine injections, autohemotherapy, the use of crude liver extract parenterally, oral and intravenous administration of nicotinic acid or its amide, low protein and acidophilus culture diet, likewise failed to give any relief.

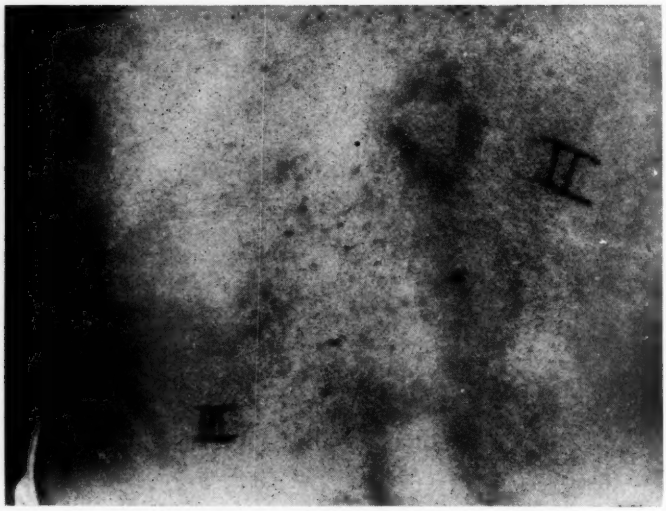

Fig. 3. The patient after exposure to a Kromyer lamp at 1 inch for thirty seconds, using three different filters, I, II, and III. Numbers I and III failed to give a reaction. Number II produced a hive with erythema, three minutes after exposure.

Passive transfer, which had been found positive in 1943, was done again. Controls, using both normal serum and saline solution, were negative (Fig. 2).

Under Dr. Lowell Erf's supervision, we attempted to see what effect autohelio transfusion would produce in the patient. A machine was used which irradiated every 10 c.c. of blood for one second with rays ranging from 2,800 A° to over 10,000 A°, with the majority of the rays being at 3,600 A°. At first only 10 c.c. of blood were withdrawn from the patient, irradiated in the machine, and then restored into the veins of the patient. Later 40 c.c. were tried and eventually 250 c.c. were used. At no time, as the result of this investigation, did the patient develop any hives, itching nor constitutional symptoms. Furthermore, there were no effects on her condition later on.

Filters to determine which rays were responsible could not be obtained. However, a few were obtained which managed to give us a fairly close idea of the range to which our patient was subject.

Figure 3 shows the patient after having used a Kromyer lamp on her skin at 1 inch for thirty seconds through three different filters. Numbers I and III failed to react. Number II gave a pronounced hive with erythema, about three minutes after exposure.

Filter No. II was a wine-colored Corning filter, No. 584, which has a range of light transmission between 3,550 A° and 3,750 A°. There is a steep rise to a peak of 3,650 A° and a steep fall to 3,750 A° (Fig. 4).

Filter No. I was a gelatin filter, No. 34, of a lavendar or purplish color. This

filter has a peak of 4,000 A°, but transmits to a minor degree between 3,000 A° and 5,200 A° (Fig. 4). It failed to produce the expected reaction.

Filter No. III was a greenish gelatin filter, No. 75, transmitting rays between 4,500 A° and 5,300 A°, with a peak at 4,900 A° (Fig. 4). It failed to produce a reaction.

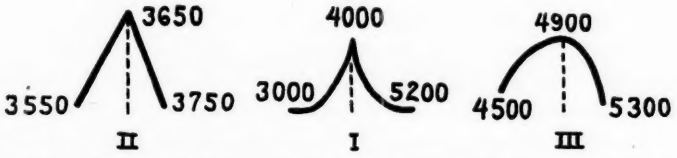

Fig. 4. Types of light transmission for filters used with Kromyer lamp as in Figure 3. Values are in Angstroms. Filter No. II produced a reaction.

The same tests were repeated using sunlight and a hot quartz lamp instead of the Kromyer lamp. The results were the same.

From the fact that our patient reacted to sunlight even through a window, although to a lesser extent, we may assume that rays above 3,000 A° are mainly responsible. The green filter, No. 75 (III), eliminated rays of 4,500 A°, as being responsible for the reaction. The results from filter No. 584 (II), definitely place most of the responsible rays at 3,550 A° to 3,750 A°. The results of filter No. 34 (I), are puzzling. Even though the peak is at 4,000 A°, the range should run down to 3,000 A°, which would permit the passage of some of the responsible rays. It is possible that not enough time was permitted to allow these diminished number of rays to pass onto the skin to provoke a reaction. If we assume that most of the rays come through this filter at the peak of 4,000 A°, we may believe our patient to be sensitive to rays approximately at a range not much more than 3,750 A° at the upper level, and probably close to 3,000 A° to 3,200 A° at the lower level.

DISCUSSION

Our patient corresponds in her sensitivity to that described by H. Blum, Baer and Sulzberger[11] who found that positive passive transfers were found in their case where the causative wave lengths were below 3,700 A°. They differentiate their case from the one described by H. Blum et al[12] where the offending rays range between 4,000 A° and 5,000 A°. In the latter condition no positive passive transfer can be obtained. They believe these are two different diseases, although still urticaria solaris; but in the range of 4,000 A° to 5,000 A° sensitivity, passive transfer failure is typical of this disease.

Here we have a new concept as to the failure or success of passive transfer. It is the actual specific sensitivity to wave lengths above 4,000 A°, in a sensitive patient, that fail to give a positive passive transfer. This is contrary to the views previously expressed by Rajka[23] who believed that positive passive transfer was only possible in a specifically strong hypersensitivity, i.e., at a high reagin titer of the blood where the reagins enter the circulation in an appreciable quantity.

Patient was then given benadryl, 50 mg. three times daily, for two weeks. It had a definite effect on her skin, reducing the amount of itching

and hives produced, and increasing her tolerance to sunlight. The effect, however, was not appreciable enough to overcome the disadvantages of drowsiness produced by the medication. At best, only about 20 per cent relief was obtained. Hence, it was discontinued. Pyribenzamine was used, without results.

Hapamine was used by Blum et al[11] with no effect.

H. Arnold[4] obtained no results with torantil in a light-sensitive case.

V. Notier[22] found about 50 per cent improvement after the use of benadryl in a case of cold urticaria, but the degree of improvement began to decrease two weeks after discontinuance of the treatment. His patient received 50 mg. benadryl four times a day for eighteen days.

Urbach and Shay[25] emphasized the fact that treatment of a hepatopathy and gastrointestinal disease may relieve a light-hypersensitive case. However, the case they describe with marked improvement of light-hypersensitivity as a result of cholecystectomy, responded slowly to sunlight, was well in the fall of the year, and the symptoms seemed to be more of a reddening of the skin, with swelling and inflammation developing after two hours, than the prompt hive developed in our case.

Lancaster[19] treated his cases of photogenic eczema and dermatitis with estrogen (and thyroid) with excellent results. Hadley[18] likewise found that injection of estrogen gave almost entire relief in his case of urticaria solaris.

However, our patient remained intractable to all forms of treatment. She does notice that she can stand sunlight better if she is near a large body of water. Also, she is a trifle better after tanning and repeated exposures in small doses to the sunlight or sunlamp. The application of a lotion or powder, which would filter out her offending rays only, i.e., at a range of approximately 3,000 to 3,750 A° would seem to be the most logical and easiest form of treatment.

SUMMARY

1. The history and development of sunlight urticaria is reviewed. The controversy as to whether it is true allergy or only a photo-dynamic phenomenon is discussed. The role of successful passive transfer in this controversy is mentioned.

2. A case of sunlight urticaria, with sensitivity to rays of approximately 3,000 to 3,750 A° and with successful passive transfer, is presented.

3. The concept of Blum, Baer and Sulzberger, that positive passive transfer can be elicited only in patients sensitive to rays below 3,700 A° is corroborated.

4. The failure of all agents to relieve the patient is noted.

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319 South Fifteenth Street, Philadelphia, Pennsylvania.

STATE LEGISLATION AGAINST DOG STEALING

State legislation against dog stealing passed this year in Massachusetts and New York and pending in California, Maryland, Wisconsin, Pennsylvania, and Michigan has been labeled a propaganda trick of the antivivisection cult by Dr. Anton J. Carlson, president of the National Society for Medical Research.

"For more than 100 years it has been illegal in most parts of the western world to steal dogs," said Dr. Carlson. "This new legislation adds nothing to the protection afforded pet owners by existing laws. The only reason for the introduction of these bills has been to provide a springboard for fantastic charges by the antivivisectionists against medical and veterinary institutions."

"It seems impossible," said Dr. Carlson, "that any one could believe that universities, state and city health departments, and great hospitals would sponsor thievery. Yet," Dr. Carlson observed, "it seems that some people will believe even the most ridiculous things if they see them in print."

Dr. Carlson suggested that the best way to protect pets would be to centralize all responsibility for the administration of laws pertaining to animals in a single government agency such as the police department. "Then," said Dr. Carlson, "the pet owner would always know where to turn for help in locating a lost animal."

"From the standpoint of medical research the advantage would lie in eliminating the confusion which makes antivivisection slanders possible," said Dr. Carlson.

SPONTANEOUS FRACTURE OF THE FIRST RIB AS A COMPLICATION OF STATUS ASTHMATICUS

MATTHEW GINSBURG, B.S., M.D., F.A.C.A.
Toledo, Ohio

THE usual complications of chronic asthma are found within the confines of the thoracic cage. Rarely does one encounter a spontaneous fracture of the rib as a result of asthma. The rarity of the above finding is attested to by the fact that no cases were found in a search of the literature, yet it is almost certain that some must have been reported.

CASE REPORT

The patient, an adult white woman, fifty-nine years of age, was admitted to the hospital March 2, 1946, in status asthmaticus. She was discharged on March 29, 1946, slightly improved. During childhood and again at the menopause, she had had repeated attacks of asthma. Six months before the present admission, asthma recurred and remained persistent. She had been in another hospital for status asthmaticus for seven weeks and had improved before discharge. There was an interval of four weeks during which she was fairly comfortable preceding the present attack. The ingestion of quinine produced hives, and aspirin caused vomiting. For many years, she had had nasal polypi. One sister had asthma.

Physical examination revealed an emaciated white woman in extreme respiratory distress. She sat up in bed supporting herself with her hands by her sides. The accessory muscles of respiration were prominent. Sweating was profuse. The blood pressure was 120/84. Temperature was normal. Auscultation of the chest revealed the usual asthmatic rales. The sputum was thick and mucoid. Blood counts and urinalyses were within normal limits. She complained of aching pains in the right side of the neck, which first began shortly before the present admission to the hospital. An x-ray of the neck and upper chest revealed the presence of a recent fracture of the left first rib, 2 inches from the spinal column (Fig. 1). The location of the pain did not fit in with the site of fracture so a repeat x-ray was ordered, and again the left first rib was reported as fractured. It is difficult to account for the pain being on the right side when the fracture is on the left, unless it is referred. The patient gave no history of an injury or fall.

A review of the anatomy[2] of the thoracic cage and the physiology[1] of respiration is apropos at this time. The first rib is flat and not twisted. The muscles attached to the superior surface are the scalenus anticus and medius and the serratus magnus. The external intercostal muscle is attached to the inferior surface. There is a fairly deep groove between the scaleni muscles wherein lies the subclavian artery; this, therefore, is structurally a weak point. The scaleni muscles raise the first rib during inspiration. The thoracic lid is formed by the first pair of ribs and the manubrium sterni. It is joined posteriorly to the spinal column and anteriorly to the sternum by the manubrio-sternal joint. During elevation of the thorax, in inspiration, the thoracic lid moves as a single piece upon the body of the sternum, assuming a more horizontal position. The manubrium is pushed forward and upward. The extent of the upward move-

ment varies in different individuals and with the depth of inspiration. Elevation of the ribs is effected by the external intercostal muscles, the fibres of which pass obliquely downward and forward from the inferior border of one rib to the superior border of the rib below. When the

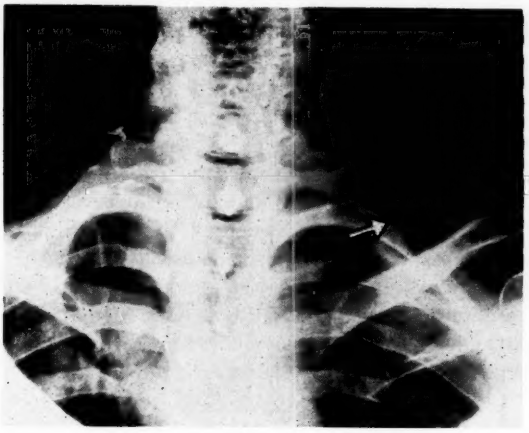

Fig. 1. Arrow indicates fracture of left first rib.

muscle contracts it exerts a pull upon these attachments which tends to depress the upper rib of the pair and raise the lower. The first rib, however, acts through the contraction of the scaleni muscles as a fixed point above, so that contraction of the external intercostals can only result in an elevation of the ribs.

It is conceivable that contraction of opposing muscles, i.e., the scaleni above and the external intercostals below, was enough to fracture the first rib.

SUMMARY

Spontaneous fracture of a rib occurring in asthma is rare. Violent, persistent contraction of opposing muscles is offered as a possible explanation.

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ALLERGIC DERMATITIS FROM VAGINAL ABSORPTION OF SENSITIZERS (Floraquin and Verazeptol)

Report of Cases

BOEN SWINNY, M.D., F.A.C.A.
San Antonio, Texas

THE cause of a considerable number of cases of dermatitis has been overlooked because of failure, in taking the drug history, to inquire specifically about the use of douches and suppositories. Patients are prone to overlook these when asked what drugs they are taking, as they think only of those ingested.

Floraquin suppositories (diodoquin, 5, 7-diiodo-8-hydroxyquinoline) are widely used in the treatment of trichomonas vaginitis. Verazeptol powder, containing chlorthymol, eucalyptol, menthol, phenol, zinc sulphate and boric acid, is widely used in cleansing douches. Search of the literature has revealed no previous reports of sensitivity to either of these preparations. Gaul[1] has reported a case of dermatitis medicamentosa from the intravaginal use of Floraquin. In his case contact test with Floraquin was negative.

CASE REPORTS

Case 1.—Mrs. J. R., aged thirty-five, with areas of pruritic maculopapular eruption about her scalp margin and the "V" of her neck, of two weeks' duration, had been using Floraquin suppositories prescribed by her physician for trichomonas vaginitis one month before. A contact test with Floraquin after twenty-four hours gave a positive reaction duplicating the original lesions. Because of the possibility that this reaction was irritative, contact tests were done on three normal controls; there were no reactions in the controls.

Case 2.—Mrs. F. A. K., aged thirty-five, had a pruritic maculopapular dermatitis across the epigastrium and over the inner aspects of both mid-thighs, of three years' duration. The food, drug and environmental history gave no clues, except she was aware that she was sensitive to ammoniated mercury ointment, which was confirmed by a patch test with the 2 per cent ointment. Other contact tests were done with rayon, wool, nylon, soap, zinc sulphate, nickel sulphate. A strong positive reaction was obtained with zinc sulphate 5 per cent, with negative reactions to the others. In searching for exposure to zinc and mercury, we finally uncovered the fact that she had been using Verazeptol douche powder for many years. A contact test with Verazeptol 10 per cent was positive on her and negative on three controls. The other substances, chlorthymol 1 per cent, eucalyptol 1 per cent, menthol 1 per cent, phenol .25 per cent, boric acid (saturated solution) present in Verazeptol gave negative tests. Ten days after ceasing the use of Verazeptol, the skin cleared and has remained clear in three months.

COMMENT

Although the vagina in both cases was the organ of absorption of the sensitizers, the mucous membrane in each case was entirely normal.

REFERENCE

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225 Medical Arts Building

Department of Clinical Pathology and Laboratory Procedures

THE COMPARATIVE DIAGNOSTIC EFFICIENCY OF THE SEDIMENTATION RATE AND THE WELTMAN REACTION

L. O. DUTTON, M.D., F.A.C.A.
El Paso, Texas

FOR some time we have been determining the sedimentation rates and Weltman reactions almost routinely in the study of allergic patients. A note was recently published in the ANNALS OF ALLERGY concerning the the technique and interpretation of the Weltman reaction.[1] It has been our impression that there is close agreement between the two tests, in a positive direction, in those patients who obviously suffer from infection. Likewise in a group of patients who obviously suffer from a simple and uncomplicated allergy, there is close agreement in the negative direction.

There has been, however, a middle group of patients in whom there was considerable doubt as to the presence or absence of infection or allergy, or the relative importance of the two if they existed simultaneously. In an effort to evaluate the relative efficiency of these two tests in this group of borderline patients, they were subjected to rather careful study and continued observation subsequent to treatment. All of these patients had been referred in an effort to determine their allergies since a clinical diagnosis had previously been made. There were forty-three patients in this group. The diagnosis of hay fever was made in thirteen instances, asthma in twenty-six instances, gastrointestinal allergy in two instances and chronic urticaria in two instances. These referred patients had received previous treatment of some kind, and the majority had been subjected to an allergy investigation.

The actual clinical existence of an infection in these patients was established by history, complete physical examination, cytological study and culture of the sputum and/or the nasal secretions, x-rays of the chest and sinuses and other organs when indicated, as well as their clinical course and response to therapy. By these methods it was established that of this group of forty-three individuals, thirteen showed symptoms whose causative factors were considered entirely of an allergic nature. Ten of the forty-three apparently suffered from an infection only. Seventeen were considered as chronic allergies with a superimposed infection. The sedimentation rates and Weltman reactions in these respective groups were as follows: (Sedimentation rates of more than 20 millimeters in one hour and Weltman bands of less than 6 were considered abnormal.)

Group 1.—Allergic manifestations only—thirteen individuals. High sedimentation rate, exudative Weltman—no cases. Normal sedimentation rate, exudative Weltman—two cases. High sedimentation rate, normal Weltman—five cases. Normal sedimentation rate, normal Weltman—six cases.

Group 2.—Individuals exhibiting infection only—ten individuals. High sedimentation rate, exudative Weltman—six cases. Normal sedimentation rate, exudative Weltman—four cases. High sedimentation rate, normal Weltman—no cases. Normal sedimentation rate, normal Weltman—no cases.

Group 3.—Individuals exhibiting both allergy and infection—seventeen individuals. High sedimentation rate, exudative Weltman—ten cases. Normal sedimentation rate, exudative Weltman—six cases. High sedimentation rate, normal Weltman—one case. Normal sedimentation rate, normal Weltman—no cases.

Group 4.—Unclassified cases—three individuals. High sedimentation rate, exudative Weltman—no cases. Normal sedimentation rate, exudative Weltman—three cases. Normal sedimentation rate, normal Weltman—no cases. High sedimentation rate, normal Weltman—no cases.

Upon examination of these results, it will be seen that in Group 1 (allergic individuals only) the Weltman reaction showed an exudative reaction in only two cases. In both these the degree of the reaction was only slight, one having a Weltman band of 5 and the other a Weltman band of 5½. In the remaining eleven individuals the Weltman reaction was completely normal but the sedimentation rate showed an increased rapidity of 20 millimeters or more in five. The cause of the increased sedimentation rate in five of this group is not clear since there was no demonstrable infection or other condition to explain it. Obviously entire dependence upon the sedimentation rate without simultaneously determining the Weltman reaction would be misleading.

In the second group of ten patients or those apparently with infection only, six showed an increased sedimentation rate and a positive Weltman reaction (most of the bands being in the region of 2, 3 and 4). In four the sedimentation rate was normal, although the Weltman reaction showed a definite exudative phase with a reading less than 6. In this group there were no Weltman reactions that did not confirm the clinical diagnosis. However, there was a normal sedimentation rate in four, and dependence on this test alone would have been misleading.

Of the third group of seventeen patients who manifested both infection and allergy, ten showed an agreement between the sedimentation rate and the Weltman reaction. The sedimentation rate was rapid and the Weltman reaction well below 6. Six had a normal sedimentation rate but an exudative Weltman reaction. In this group the sedimentation rate alone would have been misleading, whereas the Weltman reaction in one would have been deceiving. None in this group had both a normal sedimentation rate and normal Weltman reaction.

There were three unclassified cases, all of whom showed a normal sedimentation rate and a slightly exudative Weltman reaction, the values being 5 or 5½.

(Continued on Page 494)

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

FURTHER COMMENT ON DRUGS CLASSIFIED AS ANTIHISTAMINICS

Previous comments in these columns have emphasized the fact that drugs classified as antihistaminics, such as Benadryl and Pyribenzamine, have profound hypnotic effects. The clinical results, therefore, are not unequivocal as far as their antihistaminic action is concerned. Further data published in recent months by Levy and Seabury show that spirometric studies performed on sixteen patients, thirty minutes and one hour following the administration of 100 mg. of Benadryl orally, reveal no consistent tracings in the vital capacity, tidal air, minute ventilation, expiratory differential, respiratory rate or degree of emphysema. However, following the administration of epinephrine and aminophylline to five of these sixteen patients, there was a uniform increase of vital capacity, tidal air, minute ventilation, expiratory differential without any increase in the respiratory rate. Although six of the patients derived subjective benefits with decrease in dyspnea following the use of Benadryl, it is well known that sedation may produce the same effect. Indeed, in three of these patients with subjective benefit, spirometric data were directly opposed to the subjective reports. Further evidence that the so-called antihistaminic effects are not connected with the allergic state is to be found in the report of Schiller and Lowell. Brown and his co-workers had shown that a reduction in vital capacity occurs during the pollen season in cases of hay fever. Schiller and Lowell studied the reduction in vital capacity following inhalation of nebulized extracts of pollen in certain asthmatic subjects. These changes in vital capacity can be readily reproduced. The symptoms and signs which accompany such reductions in vital capacities resemble in many respects naturally occurring asthma. Schiller and Lowell dealt with the effect of adrenaline, aminophylline, atropine and Pyribenzamine on the modification of the reaction to inhaled pollen extracts as measured by changes in vital capacity. The effectiveness of the drugs studied in preventing or relieving induced reductions of vital capacity corresponds well with the known effects of these drugs in relieving spontaneously occurring asthma. The tests done with atropine and Pyribenzamine were of special interest. For example, in one patient it was shown that neither Pyribenzamine nor atropine influenced the reaction to inhaled pollen although the reduction in vital capacity following the inhalation of histamine was readily prevented by Pyribenzamine. The results of Schiller and Lowell indicate

that neither histamine nor acetylcholine play a determining role in the production of pollen asthma in the particular subject studied.

Most significant is the report of Guy on the effect of Pyribenzamine on the tuberculin reaction in man. Four hundred mgs. of Pyribenzamine per day were administered to five subjects, and the effect of tuberculin on the skin was studied following the injection of old tuberculin. Only those subjects who showed no significant degree of variation in their response to three consecutive series were selected for studies of Pyribenzamine. One hour before the injection of the tuberculin, 150 mgs. of Pyribenzamine were given to each subject by mouth. During the forty-eight hours following the injection, each subject received a total of 650 mgs. of Pyribenzamine in divided doses. The results showed unequivocally that there was no regularly significant effect on the degree of response to the tuberculin.

All of these data indicate that the use of Benadryl and Pyribenzamine as antihistaminics may well be justified where it is quite certain that histamine is the causative agent. However, in many allergic reactions, such as pollen asthma and the tuberculin type of skin reactions as indicated in the foregoing, the use of Benadryl and Pyribenzamine must be on a different basis. If it is desired to employ these drugs because of their hypnotic effects, we should certainly do so. We must understand, however, that we are not using the drugs as antihistaminics but as hypnotics. If we recognize this fact and use these drugs for their hypnotic action, the rationale of the procedure is based on logic, not on the histamine theory, the basic structure of which is extraordinarily weak in so many respects.

CLINICAL PATHOLOGY AND LABORATORY PROCEDURES

(Continued from Page 492)

From these observations it would seem that the Weltman reaction is somewhat more efficient than the sedimentation rate as a diagnostic aid. This is particularly true in borderline cases. We believe that these two tests, the Weltman reaction particularly, are valuable aids when determining those patients who have either a primary or complicating infection.

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✶ *In Memoriam* ✶

ALFONSO GRANA, M.D., F.A.C.A.

We announce with sadness the sudden death of Alfonso Graña, August 26, 1947, at Montevideo, Uruguay.

Alfonso Graña was born in Rocha, Uruguay, on June 3, 1912. He graduated from the Montevideo University High School in 1932 and from the Medical School of the University of Montevideo in 1940. He took postgraduate studies at the Allergy Clinic in the Allergy Center of the Clinical Hospital of Buenos Aires in 1941 and did experimental allergy in the Institute of Biology in Sao Paulo, Brazil, in 1944.

Doctor Graña was Chief in Internal Medicine, Faculty of Medicine, Montevideo, Uruguay, 1941-1944 (Clinic of Professor J. C. Garcia Otero). He was also Chief of the Nutrition Clinic, Department of Allergy (Clinic of Professor Beguino Varela Fuentes), Montevideo, Uruguay, Faculty of Medicine.

Doctor Graña was appointed Assistant at the Institute of Experimental Medicine of the Mayo Foundation, Guggenheim Fellowship in 1945. At the Mayo Foundation he worked under the direction of Drs. F. C. Mann and H. E. Essex. One of the articles giving the results of his experiments at the Mayo Clinic, "Experimental Purpura and Pancreatic Necrosis Produced by Forssman Heterophil Antibody," was published in the Proceedings of the Staff Meetings of the Mayo Clinic (21:298, 1946). Another article, "Blood Platelets in Heterophil Anaphylaxis," was published in the Proceedings of the Society of Experimental Biology and Medicine (61:192-195, 1946). He also read a paper before the annual meeting of the American College of Allergists in San Francisco, June 28, 1946. This paper, entitled "Influence of the Liver in Anaphylactic Shock and Experimental Study," appeared in the ANNALS OF ALLERGY (4:261, 1946). Altogether, Doctor Graña published ten papers on hydatid allergy, four papers on anaphylaxis and two books. He coauthored "Alergia en la Practica Clinica" with Professor B. Varela Fuentes and Dr. R. P. Recarte (Espasa-Calpe, Argentina, S. A., Buenos Aires—Mexico, 1946).

Doctor Graña had many friends in the United States, both in the College and at the Mayo Clinic, where he was held in esteem for his experimental researches of a fundamental nature. Doctor Graña was unmarried. His many friends in the United States join in the sorrow of his colleagues in South America.

F.W.W.

SOUTHEASTERN ALLERGY ASSOCIATION

The third annual meeting of the Southeastern Allergy Association will be held in Richmond, Virginia, on January 17 and 18, 1948, at the Jefferson Hotel.

The president of the Association is Dr. J. Warrick Thomas, 201 W. Franklin Street, Richmond, Virginia and the secretary-treasurer is Dr. Katharine B. MacInnis, 1515 Bull Street, Columbia, South Carolina.

News Items

1948 MEETING OF THE AMERICAN COLLEGE OF ALLERGISTS

The Fourth Annual Meeting of the American College of Allergists will be held at the Hotel Pennsylvania, New York City, Friday, Saturday, and Sunday, March 12, 13, and 14, 1948. Members will soon be receiving room reservation cards for the Hotel Pennsylvania, and are urged to fill in these cards and mail them immediately, as all reservations will be made directly with the hotel by those attending this meeting.

There will be no scientific or industrial exhibits. The three days will be devoted entirely to an intensive scientific program with panel discussions as formerly. There will be no charge for registration. The Registration Desk will be open on Thursday afternoon, March 11. Everyone is welcome, both members and non-members, but all must register upon arrival and receive their badges. All Fellows and Associate Fellows must present their membership cards at the desk. There are no scheduled luncheons—the Annual Banquet will be held on Saturday evening, March 13.

Plans are being formulated by the Program Committee for three topics which will bring to focus certain important aspects of allergy at this time. As usual, these topics will embrace controversial subjects, about which a good deal, however, is known. They are: (1) Mold Allergy; (2) Rhinolaryngological Allergy; (3) Neuro-Allergy.

It is of special importance to note that the third topic, Neuro-Allergy, will be the subject of intensive research during the coming year. It is with a good deal of pleasure, therefore, that the College announces specific plans for the presentation of scientific developments along this line.

The Program Committee urges all Fellows and Associate Fellows who plan to submit papers for consideration to do so by December 1, 1947. Papers should be sent to Dr. Harold A. Abramson, 133 East 58th Street, New York 22, New York. It is necessary to have them in by December 1 in order that the program may be published in the ANNALS OF ALLERGY. All papers should be sent in duplicate, 250 words in length abstracted. Papers may also be presented *by title*. There is no limit to the papers *by title* which anyone can submit and be assured of their publication in the ANNALS, if accepted. However, only one paper of this type from each author may be presented at the meeting. All papers presented *by title* will appear as part of the regular program, thus assuring the author priority. Abstracts of the papers presented *by title* will be published in the ANNALS, with the papers which are actually given at the meeting. Presenting a paper *by title* does not obligate the author to attend the meeting.

All members have received a card for membership recommendation. Names proposed for Fellowship should be mailed to the office of the Secretary. Associate Fellows may also propose membership. Application blanks will then be mailed to those whose names are submitted, the forms to be filled out and returned, together with the recommendation of a sponsor and two other letters of endorsement.

Requirements for Active Fellowship

The requirements for Active Fellowship and for promotion to Active Fellowship are:

1. All candidates must have been graduated from a reputable medical school for at least five years.

2. The candidate must furnish evidence of having applied proper allergy procedures to his practice for at least three years.

3. Evidence must be furnished of proficiency as practitioners, teachers, or research workers in organized branches of medicine, or in the field of allergy.

4. Published original works on allergy or allied subjects, or evidence of research in allergy now in progress but not yet published.

5. Evidence of training in allergy in out-patient clinics and hospitals or in the private clinic of the well organized specialist in allergy.

Associate Fellows—Any Associate Fellow seeking Active Fellowship must meet at least three of these requirements. Those who believe that they have these qualifications should submit them, together with evidence of work done satisfactorily, before being elected to Associate Fellowship. Those seeking promotions should send additional qualifications to the Secretary one month before any meeting of the Board of Regents, or one month before the Annual Meeting.

Sustaining Members

An interesting feature of membership now successfully launched by the College is a group known as Sustaining Members. A very substantial list of Sustaining Members will soon appear in each issue of the ANNALS OF ALLERGY. The establishment of a sustaining membership has been the custom of a number of scientific organizations for some time. For instance, the Society of American Bacteriologists publishes a list of seventy business concerns in their official organ, the *Journal of Bacteriology.*

The majority of these business firms, which include the manufacturers of drugs, pharmaceuticals, biologicals, scientific apparatus, and other products of interest, directly or indirectly, to the allergist or immunologist, now have well-organized staffs of research workers composed of some of the most outstanding scientists in their fields. With the best of equipment and co-ordination, these laboratories are contributing invaluable information and aid to the physician in all specialties and are ready to co-operate with the individual engaged in private research or with medical societies. It is logical that these firms associated with the allergists, both in a business and a co-operative way, be recognized as Sustaining Members.

All Sustaining Members will be listed in each issue of the ANNALS OF ALLERGY. They will also receive subscriptions to the ANNALS OF ALLERGY for their libraries. Members of their scientific staffs may attend the annual meetings of the College and may present a paper upon approval by the Program Committee. Sustaining members will also be listed in the programs of Annual Meetings and will be given priority for space and location at any scientific exhibits of any College meeting. A committee appointed by the Board of Regents passes upon the eligibility of Sustaining Members. Annual dues for a Sustaining Member is $50.

AMERICAN SOCIETY OF OPHTHALMOLOGIC AND OTOLARYNGOLOGIC ALLERGY

The American Society of Ophthalmologic and Otolaryngologic Allergy held its annual meeting at the Palmer House, Chicago, Illinois, Saturday, October 11, 1947. This meeting was dedicated to the President and Founder of the Society, Dr. French K. Hansel, F.A.C.A., St. Louis, Missouri. Dr. Hansel presented two papers; namely, "Skin Testing and Evaluation" and "Results of Clinical Investigation of Oral Ragweed Therapy." Dr. Fred W. Wittich of Minneapolis was elected the first Honorary Fellow of the Society.

During the 1946 meeting of this Society in Chicago, a group of its members proposed and adopted the plan of establishing the Hansel Foundation. In February, 1947, a charter was granted to the Foundation by the State of Missouri. The object of the Foundation is to promote further education and research in this special field of allergy. The Society already has seventy-eight members, and the interest, support and enthusiasm which have been exhibited by the members assure

the prospect of fulfillment of the aims and purposes of the organization. The officers of this Foundation include Dr. French K. Hansel, F.A.C.A., Director; Dr. W. Byron Black, F.A.C.A., President; Dr. Rea E. Ashley, Vice President; and Dr. Walter E. Owen, F.A.C.A., Secretary-Treasurer.

INTERNATIONAL ASSOCIATION OF ALLERGISTS

Dr. Paul Kallós, Helsingborg, Sweden, who is a member of the Executive Committee of the International Association of Allergists, has just completed a trip through Holland and Switzerland in behalf of the Association. As a result of Doctor Kallós' trip and recommendations, the Executive Committee of the International Association of Allergists has elected the following scientists in Switzerland to Active Fellowship in the Founders Group.

Prof. W. Löffler, Medical Clinic, University Hospital, Zurich.

Prof. W. Lutz, Dermatological Clinic, University Hospital, Basel.

Prof. A. Grumbach, Bacteriological Institute, Gloriastrasse 32, Zurich.

Prof. A. Gigon, Schweiz. Akademie f. Med. Wissenschaften, Hebelstrasse 1, Basel.

Prof. K. Bucher, Pharmacological Institute, University Hospital, Basel.

Asst. Prof. E. Hanhart, Medical Clinic, University Hospital, Zurich.

Professors Werner Jadassohn and Rolf Meier of Geneva and Basel, respectively, already belong to the International Association of Allergists.

In Holland the following have been elected:

Prof. P. Formijne, Head of the Medical Clinic, Wilhelmina University Hospital, Amsterdam.

Prof. Adrianus de Kleyn, Head of the Otological Clinic, Wilhelmina University Hospital, Amsterdam.

Prof. C. P. Prakken, Head of the Dermatological Clinic, "Binnen Gasthuis" University Hospital, Amsterdam.

Asst. Prof. H. A. E. van Dishoeck, Head of the Out-Patient Department for Allergic Diseases of the Otological Clinic, Wilhelmina University Hospital, Amsterdam.

Dr. C. Postma, M.D., Consulting Dermatologist, Wilhelmina University Hospital, Amsterdam.

Dr. W. Kremer, M.D., Head of the "Allergy Clinic of Amsterdam," Emmastraat 28, Amsterdam.

Dr. S. P. Klein, M.D., Associate of the "Allergy Clinic," Emmastraat 28, Amsterdam.

Dr. J. Bartels, Otological Clinic, Wilhelmina University Hospital, Amsterdam.

Dr. H. C. Olislagers, Medical Clinic, Wilhelmina University Hospital, Amsterdam.

Plans are now being made with S. Karger, medical publishers of Basel and New York, to publish an *International Archives of Allergy*, which will be the official journal of the International Association of Allergists. The Editorial Board will consist of internationally known scientists representing the various specialties of medicine to which allergy and immunology are applied. The publication will be quarterly and the articles may be published in the respective language of each country.

ASTHMA THROUGH THE AGES

This was the name given to a most interesting exhibit shown at the recent meeting of the American Medical Association. It was prepared by one of the past presidents of the College, Dr. Leon Unger, and his associates, Herman A. Levy, Albert H. Unger, and Isabelle Brandt Eisele of Northwestern University Medical School and Wesley Memorial Hospital, Chicago.

Murals which illustrated the highlights in the history of the study of asthma were exhibited. One scene was from the ancient and medieval period to 1500 A.D.; one from the preindustrial period (1500-1900 A.D.); and two from the modern and contemporary periods since (1900 A.D.). Portraits of twenty men who were pioneers in the study of asthma, with a list of contributions of each, were also shown. The exhibit demonstrated present views regarding etiology, pathology, diagnosis, prevention and treatment of bronchial asthma. The education of the physician and the public was stressed. The display included preserved emphysematous lungs, and chest x-ray films of asthma and its complication. Reprints and information leaflets which deal with etiology, diagnosis, differential diagnosis, treatment and results of treatment were distributed.

This exhibit will be shown for three months at the Dallas Texas Health Museum and will also be a part of the October meeting of the Wisconsin State Medical Society in Milwaukee.

The exhibitors are to be congratulated, for contributions of this type do much to educate both the medical profession and the public to the importance of allergy.

FALL INSTRUCTIONAL COURSE GRANTS

The College gratefully acknowledges the following contributions for scholarships at $100 a registrant for the Fall Instructional Course in Allergy held at the University of Cincinnati Medical School, Cincinnati, Ohio, November 3-8, 1947:

Anonymous	$500
Marcelle Hypo-Allergenic Cosmetics, Chicago, Illinois	300
Almay, Inc., New York, New York	200
E. A. Brown	100

The Scholarship Committee awarded the scholarships to the following men: John Argabright, Fred D. Droege, Benigno Garat, W. R. Katzenmeyer, Joseph Kessler, Jacques Leger, Harry C. Shirkey, A. B. Vicencio, A. S. Weiland, Jacques Sclafer.

SOUTHERN SWEDISH ALLERGY FORUM

The Southern Swedish Allergy Forum, which exists in close contact with the University of Lund, joined the International Association of Allergists last August. The Board of Regents are: Prof. Goesta Dohlman, head of the Otolaryngological Clinic of the University of Lund, chairman; Dr. Hjalmar Koch, assistant in the Department of Otolaryngology, University Hospital (Lund), secretary, and Dr. Paul Kallós, F.A.C.A. (Hon.), Helsingborg, Sweden, member Executive Committee, International Association of Allergists, Editor of "Progress in the Science of Allergy." Professor Dohlman is a member of the Board of Regents of the International Association.

We take pleasure in announcing the appearance of the new journal *Alergia*. This is published every four months, Volume 1, Number 1 covering the months of March through June. The publication is intended principally for those who are not allergists and is a synthesis of clinical and laboratory investigations in the field of allergy in the Argentine. The directors are: Doctors Guido Ruiz Moreno, Jose F. Dumm, Miguel A. Solari, Vincente Galvagno and Caupolican Castilla, all of Argentina. The subscription price outside the Argentine is eight pesos and may be obtained by writing to Maria C. Aznarez De Lothringer, Anchorena 1338—3er. piso, Dpto. B—Buenos Aires.

Publication of Fortschritte der Allergielehre Vol. II on Progress in the Science of Allergy has been announced. This volume is edited by Dr. Paul Kallós of

Helsingborg, Sweden, and published by S. Karger, medical publishers of Basel and New York. The following are the contributors: Harold A. Abramson, New York; Karl Bucher, Basel; Robert A. Cooke, New York; Liselotte Deffner-Kallós, Helsingborg; French K. Hansel, St. Louis; Holger Haxthausen, Copenhagen; Elvin A. Kabat, New York; Paul Kallós, Helsingborg; Foster Kennedy, New York; Hjalmar Koch, Lund; Rolf Meier, Basel; Frank Simon, Louisville; Lewis Stevenson, New York; Fred W. Wittich, Minneapolis.

Hyman Miller, M.D., F.A.C.A., announces the association of Ben C. Eisenberg, M.D., in the practice of Allergy, 201 South Lasky Drive, Beverly Hills, California.

M. Coleman Harris, M.D., F.A.C.A., 444 North Bedford Drive, Beverly Hills, California, has recently been promoted to Associate Clinical Professor of Medicine in the Department of Medicine (Allergy) at the College of Medical Evangelists, Los Angeles.

Dr. Benigno Garat, Buenos Aires, Chief of the Section of Allergic Diseases and Director of the Institute of Allergic Diseases of the Argentine, a Fellow of the College and the International Association of Allergists, is visiting the leading allergy clinics in the United States and Canada. Dr. Garat spent a week at the headquarters of the College and the International Association in Minneapolis.

Dr. Marion B. Sulzberger and Dr. Rudolf L. Baer announce that as of September 15, 1947, they are no longer associated in the private practice of dermatology. Doctor Sulzberger will continue his practice at 999 Fifth Avenue, New York 28, New York, and Doctor Baer will continue his practice at 962 Park Avenue, New York 28, New York.

Dr. Harold H. Golz, formerly of Clarksburg, West Virginia, has been appointed medical consultant to the Arabian American Oil Company. His new address is: Dr. Harold H. Golz, c/o Arabian American Oil Company, Dhahran, Saudi, Arabia.

Warren F. Kahle, M.D., F.A.C.A., announces the removal of his office to Suite 720, Medical Arts Building, Houston, Texas. His practice is limited to Internal Medicine and Allergy.

Arnold S. Greenberg, M.D., announces the opening of his offices at 1925 Eye Street, Northwest, Washington 6, D. C.

George J. Seibold, M.D., announces reopening of offices at 1310 Ninth Street, Wichita Falls, Texas.

Tell Nelson, M.D., former member of the Board of Regents, announces the opening of offices at King Kalakaua Building, 1415 Kalakaua Avenue, Honolulu, Hawaii. Practice limited to Allergy.

Roy A. Ouer, M.D., announces the opening of new offices at 2405 Fourth Avenue (corner Kalmia), San Diego, California. Practice limited to Internal Medicine (diagnosis and allergy).

BOOK REVIEWS

OFFICE IMMUNOLOGY. Including Allergy. A guide for the Practitioner. Edited by Marion B. Sulzberger and Rudolf L. Baer. 420 pages, 8 chapters, 26 tables, 16 illustrations. Price $6.50. Chicago: Year Book Publishers, Inc., 1947.

This comprehensive general practice manual has as its authors six authorities in their respective fields of dermatology, dermatologic allergy, internal medicine, allergy, pediatrics and immunology.

There has been a real need for practical detailed procedures in clinical immunology and allergy to be assembled under one cover which this manual accomplishes. The first two chapters deal with the common techniques, diagnostic procedures, prophylactic and therapeutic measures. There are complete chapters on the immunology of infections and dermatologic immunology, the immunologic management of spider, insect and snake bites, the immunologic principles of Transfusion Reactions—the Rh Factor. Respiratory allergies and miscellaneous allergies are adequately treated in separate chapters. Particulars of history taking, skin tests of all types, their interpretation and valuation, materials, how prepared or where obtained, dosages, medications, contraindications, and elimination or avoidance measures are presented with such exact directions so that reactions and errors are reduced to a minimum.

The etiological factors in drug eruptions, eczematous contact-type of allergic dermatitis, atopic dermatoses, fungus infections and their allergic manifestations are discussed in full.

The paper is of good stock, the illustrations and print are very clear and the book is of the handy desk reference size.

No physician who is applying clinical immunologic or allergic procedures in his office can afford to be without this manual.

THE 1947 YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY. By Marion B. Sulzberger, M.D., and Rudolf L. Baer, M.D. 638 pages, 13 articles, 84 figures. Price $3.75, Chicago: The Year Book Publishers, 1946.

This compact review of the literature on the subject of dermatology and syphilology continues to be of its usual high standard. Selected articles are assembled representing advances in dermatologic management with appreciation of contraindications or the inadequacies of therapeutic procedures. The general principles of the use of the antibiotics, topical applications, vitamins and hormones are reviewed. Outstanding advances in the diagnosis and treatment of dermatologic and venereal diseases by an authoritative evaluation of the many contributions adds greatly to its value.

THE 1946 YEAR BOOK OF THE EYE, EAR, NOSE AND THROAT. By Louis Rothman, M.D., Samuel J. Crowe, M.D., with the collaboration of Elmer W. Hagens, M.D. 543 pages, 103 figures. Price $3.75. Chicago: The Year Book Publishers, 1946.

This year book becomes a distinct improvement over its predecessor with important additions which bring it up to date.

The book is divided into three parts: Part I deals with sixteen articles which embrace all the diseases involving the eye, Part II contains five articles on the ear and Part III four articles on the nose and throat.

In the section on nose and throat, the sinuses and allergic conditions are presented in considerable detail from the recent literature. With the vast accumulating literature on diseases of the eye, ear, nose and throat, and the restrictions placed upon such a review by the size and format of the book, the authors are to be congratulated on its inclusiveness.

BOOK REVIEWS

ALLERGY IN THEORY AND PRACTICE. By Robert A. Cooke, M.D. 572 pages. 32 chapters. 43 illustrations. Price, $8.00. Philadelphia and London: W. B. Saunders Co., 1947.

This book, written in association with thirteen collaborators, is a comprehensive compilation and mainly represents the postgraduate teaching of allergy in New York City of the author and his associates. There are nine sections and an appendix.

Section I, on the fundamental aspects of allergy, is exceptionally good and is presented in a very lucid manner. Allergy of the various domains of the body is covered by authorities as fully as the scope of the book permits. There is also a section of detailed technics. The opinions of the contributors are somewhat arbitrary when omitting the published views of other authorities which would make the text more complete and increase its value as a reference book. The illustrations are excellent. The book is particularly compact and valuable to the advanced student of allergy.

DIAGNOSIS AND TREATMENT OF DIARRHEAL DISEASES. W. Z. Fradkin, M.D. Foreword by Burril B. Crohn, M.D., 264 pages, 114 illustrations. Price $5.00. New York: Grune and Stratton, 1947.

The contents are divided into three parts. I. General Considerations. II. Specific Diarrheal Disease. III. Diarrheal Diseases of Infants and Children. The book is a short practical conservative presentation in all of its phases of this field of gastroenterology.

Diarrheas reached increasing importance during and since the war, and newer diagnostic and therapeutic measures were developed. The author adequately covers these clinical, roentgenologic and laboratory aspects in a simple, direct, and practical manner.

There are chapters, containing illustrations, on Allergic Diarrhea and Psychogenic Diarrhea. The illustrations of protozoa and intestinal worms causing diarrhea make their identification relatively simple. The book is a practical guide for both the general practitioner and the specialist. The publishers are to be congratulated on the quality of paper and clear illustrations.

INDEX TO ADVERTISERS

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